

Metastases to the nose from clear cell renal cell carcinoma

A case report

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Abstract

Rationale: Patients with nasal metastases are seldom seen among clear cell renal cell carcinoma (CCRCC). We report a rare case presenting as a solitary nasal cutaneous nodule, and summarize the therapeutic experience of tyrosine kinase inhibitors (TKIs).

Patient concerns: A 86-year-old man with a chief complaint of continuous back pain for 3 months and discovery of a cutaneous nodule on the nose for a month visited the oncology department of our hospital. Maxillofacial computed tomography (CT) scans demonstrated a 1.5 × 0.9 cm and ovoid soft tissue density shade at dorsum of the nose. CT of abdomen revealed a 3.5 × 2.7 cm mass in right kidney and presenting an obvious heterogeneous enhancement.

Diagnoses: The pathological examination of nasal excision biopsy confirmed the diagnosis of nasal clear cell carcinoma. Immunohistochemical analysis indicated that the nasal metastatic tumor had a renal origin.

Interventions: Sunitinib at a dose of 50 mg/day was administered initially, while the serious cutaneous toxicities, especially hand-foot syndrome, occurred to the patient. Subsequently, axitinib at a dose of 5 mg twice daily was accepted as second-line treatment.

Outcomes: The nasal mass shrunked significantly after 8-week treatment of axitinib, and the primary tumor has been stable till now.

Lessons: Axitinib successfully controlled the nasal cutaneous metastasis with mild adverse reactions, and did not aggravate the cutaneous toxicities resulting from sunitinib. The incidence of cutaneous adverse events were low which had been reported by previous studies; however, it is difficult to say that axitinib is a more effective treatment modality for RCC with nasal metastases, which requires further studies.

Abbreviations: CCRCC = clear cell renal cell carcinoma, CT = computed tomography, TKIs = tyrosine kinase inhibitors.

Keywords: axitinib, CCRCC, cutaneous toxicities, nasal metastasis, shrinkage

1. Introduction

Renal cell carcinoma (RCC) is the common type of malignant tumor in the genitourinary system, the most common subtype of which is clear cell renal cell carcinoma (CCRCC), accounting for 70% to 80% of all renal malignancies.^[1] Due to the symptoms not obvious in early stage, about one-third of patients suffer metastasis at diagnosis, and lung, bone, lymph nodes, and liver are common metastatic sites.^[2,3] Partial or radical nephrectomy is most effective way for localized renal tumors. However, for metastatic RCC, there were no productive treatment modalities until the emergence of targeted therapy. Molecular-targeted

drugs, especially many tyrosine kinase inhibitors (TKIs) targeting vascular endothelial growth factor receptor (VEGFR), have developed rapidly for the past decade, which was applied to treatment of CCRCC. As a potent and selective inhibitor of VEGFRs1-3, axitinib was approved by the American Food and Drug Administration (FDA) for second-line treatment of patients with advanced RCC in 2012. Here, we report a extremely rare case of CCRCC with an isolated nasal metastasis, which shrunked quickly after axitinib therapy.

2. Case presentation

The patient provided a written informed consent for publication of the case, and the study protocol was approved by the scientific ethical committee of The First Hospital of Jilin University. A 86-year-old man with a chief complaint of continuous back pain for 3 months and discovery of a cutaneous nodule on the nose for a month visited the oncology department of our hospital on November 2017. He had a 10-year history of bronchitis, a 3-year history of coronary atherosclerosis and a 50-year history of smoking, with no history of hypertension and diabetes mellitus. The physical examination showed that a firm nodule as big as a horsebean with tenderness on the nose and percussion tenderness over right kidney region is positive. Maxillofacial computed tomography (CT) scans demonstrated a 1.5 × 0.9 cm and ovoid soft tissue density shade with an irregular edge at dorsum of the nose, mainly involving skin and superficialis subcutaneous tissue, which suggested characteristics of metastatic tumor. Plain CT of abdomen revealed a 3.5 × 2.7 cm and unclear boundary mass at

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the upper pole of right kidney. Enhanced images showed that the renal tumor compressed the pelvis and presented an obvious heterogeneous enhancement. To identify whether the cutaneous nodule on the nose was benign or malignant, a pathological examination of excision biopsy was performed, and the report confirmed the diagnosis of nasal clear cell carcinoma. Immunohistochemical analysis revealed positive for AE1/AE3, PAX-8, Vimentin, CA 9, CD 10, EMA, and Ki-67 (Fig. 1), while SMA, Syn, P 63, CD 34, CgA, HMB 45, and S-100 were negative, which indicated the nasal metastatic tumor had a renal origin. Combination of imaging and histological examination, the patient was diagnosed as CCRCC and nasal metastatic tumor.

He initially received sunitinib 50mg once a day for primary tumor and nasal metastatic lesion. However, the extremely serious hand-foot syndrome occurred from 3rd week of sunitinib

and the dose reduced to 37.5 mg/day. Unfortunately, cutaneous toxicities were aggravated gradually, leading to treatment discontinuation for 2 weeks. We subsequently adjusted therapeutic plan and axitinib was administered after communication with his family members. The nasal metastasis shrinkage was observed after 8-week treatment with initial dose of 5 mg twice a day (Fig. 2) and the primary tumor was stable. Subsequently, the dose was increased to 7.5 mg twice daily. But the patient could not bear severe fatigue caused by the high dose of axitinib. Eventually, primary dose was administered up to now, which was acceptable level. Imaging examination was performed every 8 weeks to evaluate the response of tumor. The last follow-up before submission of the paper showed that the tumor size (3.3 × 2.3 cm) remained stable according to the RECIST rules.

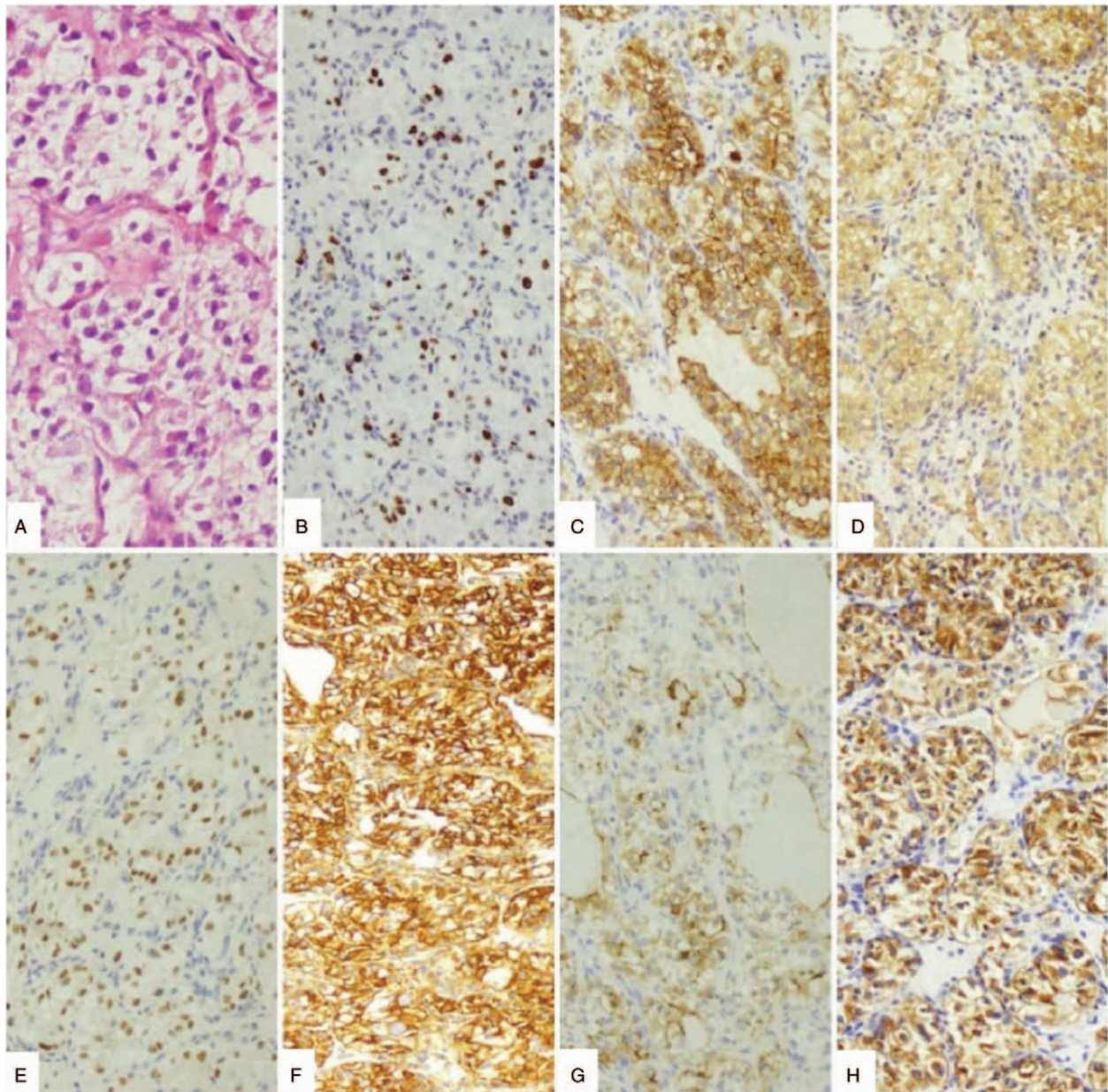


Figure 1. (A) Histopathology-nasal clear cell carcinoma H&E (magnification ×400), (B) Ki-67 (index30%), (C) CD10 (+), (D) CA9 (+), (E) PAX-8 (+), (F) Vimentin (+), (G) EMA (+), (H) AE1/AE3 (+).



Figure 2. (A) A solitary nasal cutaneous nodule as big as a horsebean. (B) Quickly shrinkage of nasal metastatic tumor after 8-week treatment with axitinib.

3. Discussion

Skin is a rare metastatic site of RCC, mainly occurring on the head and neck.^[4] The incidence of that varies from 2.8% to 6.8%.^[5] Most of cutaneous lesions are discovered after the diagnosis of primary RCC or nephrectomy, and cutaneous metastases always indicate poor prognosis. We report that the case, which presents it as a solitary cutaneous nodule on nose before the discovery of the primary tumor, is extremely infrequent.

[The von Hippel-Lindau (VHL) tumor suppressor gene alteration is observed in 80% of CCRCC cases, which induces upregulation of the hypoxia inducible factors (HIFs) through loss of VHL protein, resulting in increased expression of vascular endothelial growth factor (VEGF)]. Subsequently these changes lead to the development of RCC by angiogenesis.^[6,7] Currently, a growing number of molecule-targeting agents aiming at vascular endothelial growth factor receptor (VEGFR), mainly including sorafenib, sunitinib, pazopanib, cabozantinib and axitinib, have significantly improved patient outcomes.

Axitinib, a selective second-generation TKI of VEGFR1, 2 and 3, with half-maximal inhibitory concentrations (IC_{50}) for the VEGF family receptors considerably lower than other TKIs, while the activity of anti-Kit is weaker.^[8] The phase III AXIS trial compared axitinib with sorafenib as a second-line treatment in patients with advanced RCC.^[9] In this study, 723 patients who had progressed after the first-line therapy containing sunitinib, cytokines, bevacizumab with interferon- α or temsirolimus, were randomized to receive axitinib ($n=361$) or sorafenib ($n=362$). Both the median progression-free survival (mPFS) (6.7 months vs 4.7 months) and objective response rate (ORR) (19% vs 9%) in the axitinib group were superior to the sorafenib group. Based on this pivotal study, axitinib was approved by FDA for the second-line treatment of patients with advanced RCC. A prospective study suggested that efficacy of axitinib as second-line therapy in the real world was similar to the AXIS trial and the advantage was also revealed in further next-lines of therapy.^[10]

In addition, some studies preliminarily explored whether axitinib can be applied to patients with treatment naive. Hutson et al^[11] undertook a phase III trial evaluating axitinib versus sorafenib as first-line therapy in patients with mRCC. The investigator expected that the mPFS of axitinib group had a 4.3-month improvement comparing with the sorafenib group. Despite the result did not achieve desired purpose, the data still demonstrated the clinical activity of axitinib, prolonging 3.6 months versus sorafenib. Molecule-targeting agents combined with immune-checkpoint inhibitors is another breakthrough in treatment of advanced RCC. The JAVELIN Renal 100 trial, an open-label, dose-finding and dose-expansion, and phase 1b trial, demonstrated the efficiency and safety of the avelumab plus axitinib in treatment-naive patients with advanced RCC. In this study, 32 patients (58%) had objective responses and 45 patients (83%) experienced tumor shrinkage.^[12] Another phase 1b study exhibited that the therapeutic regimen of axitinib combined with pembrolizumab also showed antitumour activities in patients with treatment-naive advanced RCC.^[13] However, it is hard to ignore the adverse events (AEs) of combined treatment. Whether or not supply this strategy into service awaits further studies.

The toxicity of axitinib is similar to multitargeted TKIs, mainly including hypertension, fatigue and digestive troubles. In AXIS study, AEs with the rate of occurrence more than 30% was diarrhoea (55%), hypertension (40%), fatigue (39%), decreased appetite (34%), nausea (32%) and dysphonia (31%), which were manageable and tolerable by symptomatic treatment. There were no treatment-toxicity deaths in the axitinib group and only 4% of patients discontinuing axitinib due to treatment-related AEs. In addition, the incidence of hand-foot syndrome was very low, which was the primary cause of selecting axitinib in this patient. A retrospective study including 108 patients with mRCC previously receiving axitinib for ≥ 2 years found that most AEs occurred during the first 6 months of treatment, with incidence stable or decreased over time.^[14]

In this case, the patient suffered 2 grade hypertension in the initial stage of treatment, peaking at 165 mm Hg for systolic pressure and 100mmHg for diastolic pressure, but the blood pressure gradually dropped to the normal level by intervention of valsartan. Grade 3–4 fatigue occurred when the dose was increased to 7.5 mg twice a day, once seriously influencing on his daily life, but the symptom of fatigue restored gradually after adjustment of dose. Other AEs such as diarrhoea and decreased appetite were mild, and there were no laboratory abnormalities occurring in the course of treatment. To our knowledge, this is the

first case that axitinib controlled RCC with nasal cutaneous metastasis and the treatment-related adverse reactions, especially cutaneous toxicities that could be tolerated, which provides a referential case of the treatment strategy for RCC with unbearably cutaneous toxicities resulted from multitargeted TKIs.

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