

Metastatic Renal Cell Carcinoma Presenting as Painful Chewing Successfully Treated with Combined Nivolumab and Sunitinib

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ABSTRACT

Introduction: Metastatic renal cell carcinoma (RCC) to the head and neck is rare. It is the third-most common cause of distant metastasis to the head and neck, after breast cancer and lung cancer. Several drugs are available to treat metastatic RCC including high-dose interleukin and targeted therapy. Immunotherapy with nivolumab was recently approved by the US Food and Drug Administration (FDA) as a second-line treatment for patients with metastatic RCC.

Case Presentation: We present a case of metastatic RCC in a 71-year-old man with a single complaint of a 1-year history of pain while chewing food. Positron emission tomography-computed tomography showed diffuse metastatic disease. Nivolumab, off-label use before its recent FDA approval, was combined with sunitinib and resulted in an excellent and ongoing response.

Discussion: RCC is the third-most common cause of distant metastasis to the head and neck. The patient described in this case did not have any symptoms commonly seen in RCC, such as painless hematuria, weight loss, anorexia, fatigue, or anemia, despite the bulk of his disease. The other important aspect of this case is the almost complete response of his metastatic disease to the combination of nivolumab and sunitinib that was used off label before the FDA issued the approval. Future clinical trials should look at combining immunotherapy with targeted therapy in metastatic RCC.

INTRODUCTION

Renal cell carcinoma (RCC) is more common in men than in women, with an overall annual incidence of approximately 3.7%.¹ The median age of onset is around 64 years.¹ Approximately 62,000 new cases and 14,000 deaths caused by RCC occur annually.¹ Up to 30% of patients with RCC present with metastatic disease.¹ Most patients are asymptomatic until the disease is advanced. The classic triad of flank pain, hematuria, and a palpable abdominal mass is present in only 9% of patients. Several risk factors are thought to play a role in the etiology of RCC; these include smoking, hypertension, obesity, renal cystic disease, use of nonsteroidal anti-inflammatory drugs and other analgesics, chronic hepatitis C infection, and history of kidney stones.²⁻⁵

High-dose interleukin (HDIL-2) is the only therapy that provides a potential cure in a minority of patients.⁶ Several targeted therapies are approved as first-line for those

patients who are not fit for HDIL-2.⁶ The recent advent of immunotherapy with checkpoint inhibitors has brought hope to patients with metastatic renal cell carcinoma. In this case we discuss a unique presentation of metastatic renal cell carcinoma. Also we report an excellent sustained tumor response to combined sunitinib and nivolumab.

CASE PRESENTATION

A 71-year-old man presented with pain while chewing, progressively worse, during the last year. He initially saw his dentist, and an oral exam did not reveal any abnormalities. Pain medications were prescribed for use as needed. His symptoms gradually got worse, so he was referred to an otolaryngologist.

Soft tissue neck computed tomography (CT) with contrast revealed a 5-cm intensely enhancing mass with extensive vascular supply in the left masticator space (Figure 1). Fine needle aspiration of the

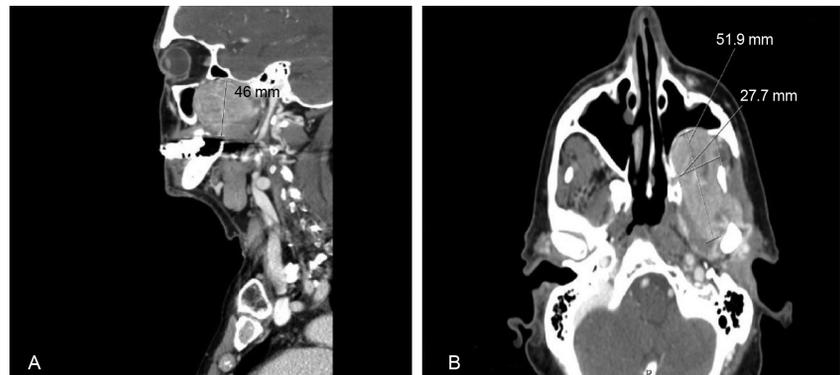


Figure 1. Soft tissue neck computed tomography revealing a 5-cm intensely enhancing mass with extensive vascular supply in the left masticator space. A. Sagittal view. B. Transverse view.

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mass showed large cells with clear vesicular cytoplasm. These cells were reactive to paired box gene 8 (*PAX8*) and pankeratin, whereas the supporting cells were reactive to smooth muscle actin. These findings were suggestive of metastatic renal cell carcinoma (RCC). Full-body positron emission tomography (PET)-CT confirmed the above findings but also revealed masses at the inferior pole of the left kidney, retroperitoneal lymphadenopathy, and bilateral lung nodules (Figure 2A). The differential diagnosis based on the location of the mass included schwannoma, hemangiopericytoma, angiosarcoma, lymphoma, and metastatic carcinoma, particularly lung carcinoma and RCC. Sunitinib, an inhibitor of cellular signaling that targets multiple receptor tyrosine kinases, was initiated at 50 mg orally daily (4 weeks on and 2 weeks off). His pain was controlled with opioids, but we discussed with him palliative radiation therapy to the left masticator space mass in case his pain became resistant to opioids. Follow up PET-CT postsunitinib therapy showed an interval progression of his disease (Figure 2B). Nivolumab, an anti-program death receptor 1 inhibitor, was not approved yet by the US Food and Drug Administration, but we decided to add it to sunitinib, and the combined treatment resulted in almost complete response (Figure 2C). Table 1 illustrates a timeline of his follow-up visits, diagnostic tests, and interventions.

DISCUSSION

Surpassed only by breast cancer and lung cancer, RCC is the third-most common cause of distant metastasis to the head and neck.⁷ Head-and-neck metastasis is the presenting complaint for 7.5% of patients with RCC.⁸ However, only 1% of patients with RCC have metastasis confined to the head and neck.⁸ A retrospective chart review of 21 cases of metastasis of RCC to the head and neck found that the most common sites of metastasis were bone (n = 6), skin and subcutaneous tissue (n = 6), and lymph nodes (n = 5).⁹ A head-and-neck metastasis may occasionally be the presenting sign in a patient with RCC or may follow the primary diagnosis by many years.⁹ Our patient did not have any symptoms commonly seen in RCC, such as painless hematuria, weight loss, anorexia, fatigue, or anemia, despite the

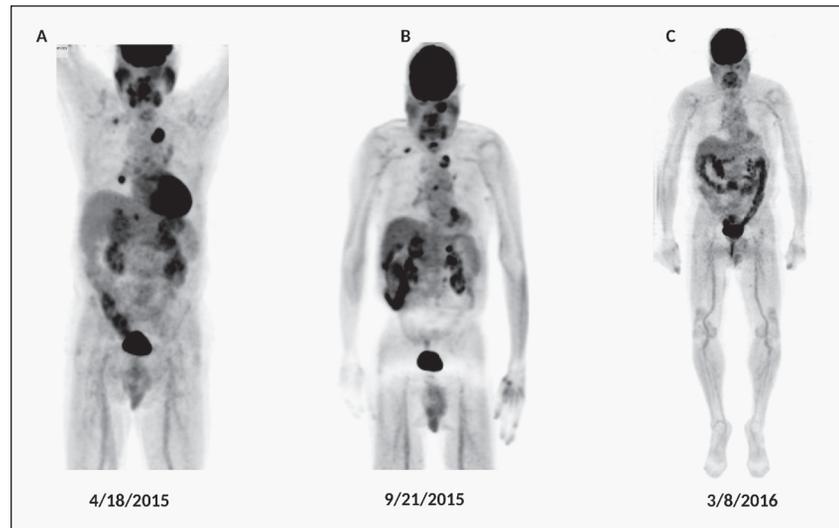


Figure 2. Sagittal positron emission tomography-computed tomography (PET-CT) scan images of full body. A. Initial PET-CT clearly showing evidence of metastatic disease. B. Progression of disease on sunitinib. C. Follow-up PET-CT scan revealing almost complete response to combined nivolumab and sunitinib.

bulk of his disease. It was only pain while chewing food that led to the diagnosis of metastatic RCC. CT scan with contrast is the imaging modality of choice in demonstrating the vascularity and extent of the lesion.⁷

The pathology revealed cells that are reactive to *PAX8* and pankeratin. *PAX8* and paired box gene 2 (*PAX2*) are transcription factors important for fetal development of several organs, including kidney, müllerian organs, brain, and eye. Both are good markers for renal cell tumors. Almost all RCCs are positive for *PAX8*, which is frequently expressed by lymphoma (100%), nephrogenic adenoma (100%), parathyroid tumors (62%), thyroid tumors (100%), and müllerian organ-derived tumors (92%).^{10,11} Tumors that may be negative or infrequently positive for *PAX2*, including chromophobe RCC, oncocytoma, and sarcomatoid RCC, are often positive for *PAX8*.¹²

Several drugs are available to treat metastatic RCC. Patients with good Karnofsky performance status ($\geq 80\%$) and intact organ function are treated with high-dose interleukin-2 (HDIL-2) up front. HDIL-2 can induce long-term remissions in approximately 10% of patients.¹² This treatment is associated with an approximately 4% mortality rate, so it is extremely important to select patients who are fit for this therapy.

Several targeted therapies were approved as first-line for those patients who are not fit for HDIL-2, but treatment is based on risk groups. The Memorial Sloan-Kettering Cancer Center prognostic score stratifies patients with metastatic RCC into poor, intermediate, and favorable risk categories on the basis of the number of adverse clinical and laboratory parameters present.¹³ Poor prognostic factors include a Karnofsky performance status of less than 80 (80 indicates normal activity with effort and some signs or symptoms of disease), time from diagnosis to treatment less than 12 months, serum lactate dehydrogenase more than 1.5 times the upper limit of normal, corrected serum calcium greater than 10 mg/dL, and hemoglobin less than the lower limit of normal.¹³ Patients in the favorable-risk group have no poor prognostic factors, those in the intermediate-risk category have 1 or 2 adverse prognostic factors, and patients with poor-risk RCC have more than 2 poor prognostic factors. Patients in the favorable or intermediate risk group are treated with sunitinib, pazopanib, or interferon alpha plus bevacizumab,¹⁴⁻¹⁶ whereas the front-line treatment for those in the poor risk group is temsirolimus alone.¹⁷ Axitinib and sorafenib has been approved as second-line treatment, for use after other targeted therapy or cytokine therapy has failed.¹⁸

Activating the immune system appears to be a promising strategy to treat metastatic RCC. Since 2011, 2 novel classes of immunotherapy drugs have been approved: the cytotoxic T lymphocyte antigen 4 (CTLA-4) inhibitor ipilimumab and the program death receptor 1 inhibitors pembrolizumab and nivolumab.¹⁹ In melanoma the combination of ipilimumab

and nivolumab resulted in an objective response rate of 61%.¹⁹

In a phase I trial, patients with metastatic RCC received nivolumab in combination with sunitinib (50 mg, 4 weeks on, 2 weeks off) or pazopanib (800 mg daily), until progression/unacceptable toxicity. The starting dosage of nivolumab was 2 mg/kg intravenously every 3 weeks with planned

escalation to 5 mg/kg intravenously every 3 weeks. Objective response rate was 52% among patients receiving nivolumab and sunitinib and 45% among those receiving nivolumab and pazopanib. Almost half the responses occurred by the first assessment, which is week 6 of treatment. The investigators concluded that nivolumab plus sunitinib or pazopanib showed encouraging

Table 1. Timeline of the case

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Date	Relevant past medical history and interventions		
April 20, 2015	<p>Chief complaint: A 71-year-old man with no past medical history presented with painful chewing during the past 1 year.</p> <p>Family history: Mother died from pancreatic cancer at the age of 69. Father died from lung cancer at the age of 86.</p> <p>Physical examination: Mild left cheek swelling.</p> <p>Previous imaging: An outside-hospital, soft-tissue neck CT with contrast dated March 12, 2015 revealed a 5-cm intensely enhancing mass with extensive vascular supply in the left masticator space.</p> <p>Previous intervention: A CT-guided biopsy of the mass dated April 2, 2015 confirmed metastatic renal cell carcinoma (clear cell type).</p> <p>Current intervention: Ordered whole-body PET-CT scan to complete the staging.</p>		
Date	Summaries from initial and follow-up visits	Diagnostic testing	Interventions
April 18, 2015	Follow-up visit	PET-CT: At least a 3.7-cm mass within the left pterygopalatine fossa, SUV 2.4. A minimum of 10 nodules are seen scattered throughout both lungs; the largest measures 33 x 28 mm, SUV 6.2. Liver: Approximately 2.1-cm focus in the posterior aspect of segment VIII, SUV 3.1. Right suprarenal fossa: approximately 9 x 6-cm mass, SUV 2.7. Left kidney, inferior pole: Approximately 9-cm mass, SUV 5.0.	Sunitinib 50 mg orally daily (4 weeks on, 2 weeks off).
May 19, 2015	Tolerating medication without problems. States that he has some left cheek swelling that comes and goes	None.	Sunitinib was approved by his insurance and shipped to patient. Medication started May 1, 2015.
July 7, 2015	Left cheek swelling that comes while off Sunitinib and goes away while on Sunitinib	PET-CT: At least a 4.1 x 2.5-cm mass within the left pterygopalatine fossa, SUV 5.5. A minimum of 10 nodules are seen scattered throughout both lungs; the largest measures 36 x 29 mm, SUV 6.3. Liver: Approximately 5-cm focus in the posterior aspect of segment VIII, SUV 5.1. Right suprarenal fossa: Approximately 10.5 x 5.4-cm mass, SUV 5.3. Left kidney, inferior pole: Approximately 6.9-cm mass, SUV 5.6. These findings are consistent with progression of his disease.	We decided to get nivolumab off label use. We told the patient to continue taking sunitinib because he had been on it for only 2 months.
August 5 - September 15, 2015	Patient was seen every 2 weeks while on nivolumab	None.	Completed 4 cycles of nivolumab.
September 21, 2015		PET-CT: Complete opacification of the left maxillary sinus, SUV 6.3. A minimum of 10 nodules are seen scattered throughout both lungs, most of which appear slightly improved; the largest measures 28 mm, SUV 5.5. There is interval improvement in previously documented hypermetabolic right hepatic focus, which on today's study has an SUV of 2.9 (prior SUV 5.1). Stable to slight morphologic and metabolic improvement in previously documented left and right renal masses.	Continue sunitinib and nivolumab, restage disease in 3 months.
December 15, 2015	Tolerating treatment well with combined sunitinib and nivolumab	PET-CT: Decreased extent and metabolic activity of left masticator space metastasis, SUV 3.7. Decreased size of the left lower pole renal mass. Decrease in size, and metabolic activity of lung, right adrenal, retroperitoneal soft tissue and lymph node metastases.	Continue combined sunitinib and nivolumab, restage disease in 3 months.
March 8, 2016	Tolerating treatment well with combined sunitinib and nivolumab	PET-CT: Improving metabolic activity in the left masticator space, SUV 2.7 (prior SUV 3.6). Stable to slight improvement in the previously documented subcentimeter right lung nodules and 1.7-cm left upper lobe mass.	Continue combined sunitinib and nivolumab, restage disease in 3 months.

CT = computed tomography; PET = positron emission tomography; SUV = standardized uptake value.

antitumor activity and a manageable safety profile in patients with metastatic RCC.²⁰ The decision to add nivolumab (off-label use) in our patient was based on the results of the above phase I trial. Three months later (November 23, 2015), the FDA approved nivolumab on the basis of results of an open label, randomized study that showed an overall survival advantage of nivolumab over everolimus in patients with metastatic RCC who failed antiangiogenic agents.²¹ Those treated with nivolumab lived an average of 25 months compared with 19.6 months in those treated with Afinitor. Additionally, 21.5% of those treated with nivolumab experienced a complete or partial shrinkage of their tumors, which lasted an average of 23 months, compared with 3.9% of those taking everolimus, lasting an average of 13.7 months.^{21,22}

Our patient appears to be tolerating the combination of nivolumab and sunitinib. His follow-up PET-CT showed improvement in his disease (Table 1).

CONCLUSIONS

Metastatic cancer to the head and neck is rare. Breast cancer, lung cancer, and RCC are the most common causes of distant metastasis to the head and neck. In our case, pain while chewing food was the only presenting symptom of metastatic RCC. Immunotherapy with interleukin-2 or interferon-alpha, biologic, or targeted therapy are all viable options for patients with metastatic RCC. Most recently the FDA approved nivolumab in the second-line setting after patients have failed antiangiogenic agents. Our patient had an almost complete response to combined nivolumab and sunitinib. Further studies should look into the combination of targeted therapy and immunotherapy in the front-line setting among patients with metastatic RCC. ❖

Disclosure Statement

The author(s) have no conflicts of interest to disclose.

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Flexibility

Fixity of purpose requires flexibility of method.

—Harold G Wolff, 1898-1962, American physician, neurologist, and scientist