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Renal Cell Carcinoma with Pulmonary Metastasis and Metachronous Non-Small Cell Lung Cancer

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Abstract

Introduction—The development of a second primary malignancy in a patient with a preexisting diagnosis of metastatic cancer may be easily overlooked or misattributed to progression of disease. We report 3 patients with clear cell renal cell carcinoma (ccRCC) metastatic to the lungs who were subsequently diagnosed with non-small cell lung cancer (NSCLC). We examined the frequency of this occurrence within our institution and report on the radiographic findings that may help distinguish between metastatic and primary lung cancers.

Methods—Patients who received systemic targeted therapy for metastatic RCC at our institution between January 2006 and October 2013 were identified and the proportion and incidence rate for developing NSCLC with pre-existing metastatic RCC were calculated.

Results—2% of patients (3/151; 95% CI 0.68 – 5.68%) treated for metastatic RCC with systemic targeted therapies at our institution were subsequently diagnosed with NSCLC, increasing to 3.5% (3/85; 95% CI 1.21 – 9.87%) among patients with known RCC pulmonary metastasis. The incident rate for development of NSCLC in metastatic RCC patients was 0.87 per 100 person-years (95% CI 0.22 – 2.4).

Conclusion—The subsequent development of a primary lung cancer in metastatic RCC patients, which occurred in 2% of patients at our institution, appears underreported in the literature. Primary NSCLC may be underdiagnosed in patients with metastatic RCC. Both the radiographic

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appearance and clinical behavior of a lesion may hold clues that can help distinguish between a new primary and progression of metastatic disease.

Introduction

Renal cell carcinoma is the 9th leading cause of cancer in the United States and is responsible for 14,000 deaths per year (2.4% of all cancer deaths).¹ 17% of patients present with metastatic disease.¹ The median survival of patients with metastatic kidney cancer, previously around 12 months prior to the development of targeted therapies, has steadily improved with the introduction of vascular endothelial growth factor receptor tyrosine kinase inhibitors (VEGF-TKIs), mammalian target of rapamycin complex 1 (mTORC1) inhibitors and most recently immune checkpoint inhibitors.^{2–4} As overall survival improves, the management of patients' other medical conditions, including new primary malignancies, becomes increasingly important. Here we describe a series of 3 patients diagnosed with non-small cell carcinoma of the lung during treatment for metastatic renal cell carcinoma, report the frequency of this occurrence within our institution, and discuss the clinical and radiographic findings which may help distinguish between metastatic disease and a new primary cancer.

Methods

After approval of the Institutional Review Board, a database of patients with metastatic renal cell carcinoma treated at the University of Texas Southwestern Medical Center (UTSW) between January 2006 and October 2013 was generated through a search of the electronic medical record by the ICD 9 diagnostic code for renal cell carcinoma. Patients who received treatment with a targeted agent and whose care was actively managed at UTSW during this period were included. Targeted agents included VEGF-TKIs, the anti-VEGF monoclonal antibody bevacizumab, or mTORC1 inhibitors. Charts were manually reviewed to confirm the diagnosis, and clinical information relevant to the patients' treatment and outcomes was collected. Overall survival and duration of follow-up were based on the initial diagnosis of metastatic RCC and the date of death, or most recent clinic encounter. For patients no longer followed in our practice, the date of death was assessed through the Social Security Death Index or local obituary records. Patients were excluded if they (i) only received surgery or radiotherapy but not a targeted agent, (ii) were not candidates for systemic treatment, or (iii) had insufficient follow-up data available, as occurred when they were only seen for a second opinion. Patients were followed until death or the most recent database update in October 2015. The proportion of patients with mRCC and a diagnosis of lung cancer compared with those without that diagnosis was calculated, with 95% confidence intervals determined by the Score method without continuity correction.⁵ The incidence rate for lung cancer in person-years and 95% confidence intervals were calculated by the Mid-P exact test. All calculations were performed using OpenEpi, version 3.0.⁶

Case 1

A 68-year-old man with a 90 pack-year smoking history and cardiovascular history notable for prior coronary artery bypass, hypertension and multiple prior strokes was found to have

with a 4.5 cm exophytic right kidney mass in July 2008. Due to its size and hilar location, a radical nephrectomy was performed demonstrating a ccRCC, Stage III (pT3a N0, Fuhrman Grade 2). A CT of the chest (Fig. 1, Case 1A) in December 2012 demonstrated bilateral pulmonary nodules (measuring up to 1.1 cm) along with a 2 cm paratracheal and 1.4 cm subcarinal lymph node. A bronchoscopic fine needle aspiration of the subcarinal lymph node demonstrated metastatic RCC (Fig 2A). The patient started therapy with the mTORC1 inhibitor temsirolimus rather than a TKI due to his cardiovascular disease. Follow-up imaging demonstrated stable disease until February 2015, when a CT of the chest demonstrated isolated progression of a right upper lobe nodule (Fig. 1, Case 1A–B) now measuring 1.5 cm. Given the spiculated appearance on CT and the isolated nature of the progression, the concern was raised about the possibility of NSCLC. Core needle biopsy demonstrated squamous cell carcinoma (Fig. 2, compare A and B). He was treated with stereotactic radiation (a total of 50 Gy in 5 fractions) as he was determined not to be an operative candidate due to his cardiovascular disease and metastatic RCC. Temsirolimus was then resumed with stable RCC disease and no evidence of the recurrent lung cancer as of February 2016.

Case 2

A 61-year-old man with a 40 pack-year history of cigarette smoking prior to quitting in 1990 and ongoing cigar smoking (3–4 per day) was diagnosed with an asymptomatic renal mass on a CT scan performed for acute diverticulitis in October 2011. MRI of the abdomen demonstrated a 10 cm upper pole left renal mass as well as a 4.1 cm contralateral right adrenal mass. CT scan of the chest demonstrated multiple pulmonary nodules (largest 1.3 cm) and mediastinal lymphadenopathy. Biopsy of the left renal mass demonstrated ccRCC (Fuhrman Grade 3). The patient received neoadjuvant everolimus on a clinical protocol (NCT00831480) and one month later had a left radical nephrectomy and bilateral adrenalectomies which revealed ccRCC in the contralateral adrenal gland. He continued everolimus postoperatively for approximately 18 months with stable disease. However, he subsequently developed Grade 2 proteinuria and gastrointestinal bleeding (later found to be secondary to a small bowel arteriovenous malformation) and everolimus was discontinued. On serial imaging, a previously identified small right upper lobe rounded nodule became spiculated, irregularly-shaped, and ultimately enlarged up to 1.3 cm in size (Fig. 1, Case 2A–C). The other pulmonary nodules remained unchanged or decreased in size during the same time interval. Given the isolated progression and imaging characteristics a biopsy was obtained, which confirmed lung adenocarcinoma. The patient underwent a robotic lobectomy and ipsilateral lymph node dissection. Mediastinal and hilar lymph nodes were involved with RCC only (Fig. 2, compare C and D). Since surgery the patient has remained off therapy and radiographic surveillance demonstrated only very slow progression of the remaining pulmonary nodules.

Case 3

A 67-year-old man who was never a smoker had a right radical nephrectomy in 2007 for a ccRCC (pT3a, Fuhrman Grade 2) and left partial nephrectomy for two pT1a ccRCCs (0.8 cm Fuhrman Grade 1, and 2.4 cm Fuhrman Grade 2). He had no evidence of metastatic

disease on serial imaging until a serious motor vehicle accident in August 2012 resulted in a prolonged hospitalization (approximately 11 months including inpatient rehabilitation). After developing pneumonia, a CT scan of the chest demonstrated a 1.9 cm spiculated nodule in the apex of the right upper lobe with associated bronchiectasis (Fig 1, Case 3A–B), which at that time was attributed to the underlying infection. However, a repeat CT scan 14 months later showed that the right apical nodule had increased to 2.2 cm (Fig 1, Case 3C–D) and there were multiple other pulmonary nodules, including a 1.2 cm pleural-based nodule in the right upper lobe. Biopsy of the more accessible 1.2 cm nodule demonstrated metastatic ccRCC (Fig 2E) and he started treatment with pazopanib. Over the course of the next 15 months there was improvement in the majority of the pulmonary nodules. The largest nodule in the right apex, however, remained unchanged in size and spiculated in appearance prompting a biopsy in February 2015, which demonstrated adenocarcinoma (Fig. 2F). A FDG PET scan demonstrated uptake in bilateral mediastinal lymph nodes, which were confirmed on bronchoscopic biopsy to be involved with lung adenocarcinoma. An MRI of the brain demonstrated numerous subcentimeter metastases. As his known metastatic RCC was continuing to respond to therapy, the brain lesions were attributed to his lung adenocarcinoma. He received whole brain radiation prior to systemic chemotherapy with carboplatin and pemetrexed, but progressed after only two cycles. He subsequently progressed on nivolumab and passed shortly afterwards.

A summary of the three cases is provided in Table 1.

Results

A total of 151 patients were identified who received systemic treatment with a targeted agent for metastatic RCC at our institution during the period from January 2006 to October 2013. Overall, 56.3% (85/151) had pulmonary metastases at the time metastatic disease was diagnosed. This rate is comparable to what is documented in previous studies.^{7,8} 2% of these patients (3/151) were subsequently diagnosed by the primary oncologist with lung cancer (95% CI 0.68 – 5.68%). Taking into account only patients with pulmonary RCC metastases the proportion increased to 3.5% (95% CI 1.21 – 9.87%). Follow-up continued until the most recent comprehensive database update in October 2015. This period encompassed a total of 343 person-years, during which the lung cancer incidence rate within our cohort of patients was 0.87 per 100 person-years (95% CI 0.22 – 2.4). 80.8% (122/151) of patients had expired and only 4% (6/151) were lost to follow-up as of October 2015. None of the other 148 patients were diagnosed with lung cancer during the period of follow-up. The median duration of follow-up, defined as time from diagnosis of metastatic disease to death or last follow-up, was 21.5 months.

Discussion

The cases above illustrate the challenge of establishing a diagnosis of a new malignancy in a patient with a previously diagnosed metastatic cancer. While they represent a single institution experience, they suggest that the occurrence of new lung cancers in patients with metastatic RCC may be underreported. A review of the literature revealed only 4 previously described cases^{9,10} The occurrence of other malignancies with RCC has been previously

reported, but to our knowledge the incidence of lung cancer in patients with RCC and pulmonary metastasis has not been documented. Patients followed after surgical resection of localized RCC do not seemingly have an increased risk of lung cancer despite an observed increased risk of bladder cancer, another smoking-related malignancy.^{11,12} However, an increased incidence of RCC following a diagnosis of lung cancer has been reported, so the relationship between these two malignancies remains unclear.¹³ In our experience, 2% of all patients with metastatic RCC and 3.5% of patients with lung metastasis were diagnosed with lung cancer during follow-up for their RCC diagnosis. While smoking status was not available for our cohort as a whole, and one patient presented above was a nonsmoker, it would be reasonable to surmise that this figure would be even higher among patients with a smoking history. Overall, these data suggest that NSCLC in patients with RCC metastatic to the lungs is potentially underdiagnosed clinically.

There is limited literature on the radiologic appearance of pulmonary metastases from RCC. The majority of patients present with small (i.e. 0.5–2 cm) nodules with well-defined smooth margins and the number of nodules may vary from a few scattered nodules to extensive involvement of both lungs (“cannonball” metastases). A study using high-resolution CT compared the margins of the lesions to autopsy specimens and found a correlation between the growth pattern and the CT appearance.¹⁴ Metastatic nodules with an alveolar-space filling growth pattern on histopathology exhibited smooth well-defined borders on CT. In contrast, tumors with an interstitial proliferative type growth pattern tend to exhibit irregular, poorly defined margins. In one series, 38% of metastatic lesions had smooth, well-defined margins on CT, including the one case of RCC.¹⁴

The CT appearance of primary lung malignancies and its correlation with histopathologic characteristics is better understood. Most malignant lung nodules exhibit spiculated margins on CT corresponding to fibrosis, localized lymphangitic spread of tumor, or an infiltrative tumor growth pattern.¹⁵ Pleural tags, such as those seen in our first and third patients, are caused by fibrotic bands usually associated with juxtacatricial pleural retraction and are more common in malignant pulmonary lesions (58%) compared to benign nodules (27%).¹⁵ The presence of patent bronchi within the lesion was readily apparent in our third patient and is also a CT finding more frequently associated to malignant lung lesions.¹⁵

Nodule growth may provide also additional information about the nature of the lesion. Most malignant nodules double in volume between 30 and 400 days although faster doubling times may occur in lymphoma and metastases.¹⁶ Similarly, infectious and inflammatory conditions may exhibit faster growing patterns. Perhaps more important is the discrepancy in the growth pattern of a single pulmonary nodule in the context of stable or decreasing metastatic lung nodules, particularly when growing nodules exhibit imaging characteristics associated with primary lung malignancies.

An additional challenge in managing patients with pulmonary nodules is the lack of consistency in reporting imaging characteristics on CT reports even in patients with single lung lesions undergoing surgical resection.¹⁷ While an irregular, spiculated margin predicts bronchogenic carcinoma in 86% of cases, only 78% of CT reports include this feature.¹⁷ This number is likely much lower in the case of patients with multiple pulmonary nodules

and clinically suspected metastatic disease. Our results emphasize the need to specifically note the presence of pulmonary nodules with irregular and ill-defined margins in patients with metastatic RCC to the lung in CT reports as these may represent primary lung neoplasms. Computer-aided detection and characterization of pulmonary nodules with prediction models have been shown to be helpful in the diagnosis and pre-surgical evaluation of pulmonary nodules^{18,19} and may help identify these lesions.

While the standard of care is to establish a pathologic diagnosis of metastatic disease at the outset, subsequent sites of progression or metastasis are often diagnosed clinically on the basis of radiographic findings. In the case of lesions with an atypical radiographic appearance for metastatic disease, or which are progressing despite stability or regression of other metastases while on therapy, the possibility of a new primary malignancy should be considered. A history of tobacco use should also increase suspicion for the co-occurrence of smoking-related malignancies.²⁰ Biopsy of a new or progressing nodule may avoid unnecessary changes in therapy, and provides the opportunity to pursue curative therapy for the early stage cancer.

Our report has several limitations. First, this is a retrospective study and our cohort was not systematically reviewed. However, the three cases of lung cancer were identified by the primary oncologist (J.B.) who followed 62% of patients. Second, this report represents the experience of a single academic center that includes a large referral population and may not represent the spectrum of patients seen in general practice.

Conclusion

The occurrence of a new lung cancer in patients with metastatic RCC is infrequently reported in the literature but in our experience is at least 2% and may be higher. Furthermore, while these cases represent a single type of secondary malignancy, we believe the principles are generalizable to any patient with metastatic disease. Patients with metastatic cancer are surviving longer, and the increased frequency of imaging tests is likely to increase the detection of new cancers. The assumption that a new or progressing lesion represents an additional focus of involvement by the same malignancy may miss the opportunity to diagnose a treatable or potentially curable new cancer.

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Clinical Practice Points

- The frequency of a new diagnosis of lung cancer in patients treated for metastatic renal cell carcinoma at our institution was 2%, and 3.5% of those with lung metastases.
- Careful attention should be given to new or progressing pulmonary nodules even in patients with known RCC pulmonary metastatic disease.
- Radiographic findings which should raise suspicion of a new lung neoplasm include a spiculated appearance, lymphangitic spread, the presence of air bronchograms or pleural tags, or nodules that exhibit growth patterns which are discrepant from other known sites of metastatic disease.

Fig. 1.

Case 1:

(A) CT scan of the chest in December 2012 demonstrating a small nodule in the right upper lobe. This nodule had a stable radiographic appearance on subsequent scans until February 2015 (B), when it increased to 1.5 cm and exhibited a more spiculated appearance. A faint pleural tag (arrowhead) was then visible. Remaining pulmonary nodules remained stable in size.

Case 2:

CT scans of the chest tracking a small rounded right upper lobe lung nodule that increased from 0.6 cm in July 2012 (A) to 1.3 cm in October 2013 (B) and January 2014 (C). Note the obvious development of spiculated and irregular shape appearance over time. Other subcentimeter nodules demonstrated stability or regression over this time interval.

Case 3:

Axial (A) and coronal reconstructed (B) CT images of the chest from September 2012 demonstrating a 1.9×1.3 cm irregularly-shaped nodule with underlying bronchiectasis. Corresponding axial (C) and coronal reconstructed (D) CT images obtained in October 2013 confirmed growth of this lesion up to 2.2 cm with an increasingly spiculated appearance. Note the increasing pleural tags superiorly (arrowheads).

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Fig. 2.

Case 1:

(A) Fine needle aspirate of a mediastinal lymph node from December 2012 demonstrating cells with nuclear pleomorphism and ill-defined clear to granular cytoplasm consistent with RCC. [Hematoxylin and eosin stain 200x with Diff-Quick stain 400x inset]. (B) Core needle biopsy of the right upper lobe lung nodule from May 2015 demonstrating squamous cell carcinoma. [Hematoxylin and eosin stain 200x with p63 immunostain inset].

Case 2:

Pathology samples from a robotic right upper lobectomy and lymph node dissection demonstrating (C) classic ccRCC histology within a station 10R lymph node staining positive for PAX8 [Hematoxylin and eosin stain 200x with PAX8 immunostain inset] and (D) adenocarcinoma within the right upper lobe which was immunoreactive for thyroid transcription factor-1 (TTF-1) consistent with a primary lung adenocarcinoma [Hematoxylin and eosin stain, 200x with TTF-1 immunostain inset].

Case 3:

(E) CT guided core biopsy of a pleural-based right upper lobe nodule (separate from subsequently diagnosed primarily lung neoplasm) from December 2013 demonstrating CD10 immunoreactive RCC. [Hematoxylin and eosin stain 200x with CD10 immunostain inset]. (F) CT guided core biopsy of the dominant right upper lobe apical nodule revealing an adenocarcinoma that was reactive for TTF-1. [Hematoxylin and eosin stain, 200x with TTF-1 immunostain inset].

Table 1

Case	Sex	Age at NSCLC Diagnosis	Smoking History	RCC Pathology	NSCLC Pathology	Sites of RCC Metastases	Time from RCC Pulmonary Metastases to NSCLC	RCC Treatment	NSCLC Treatment	NSCLC Best Response to Treatment	Survival Since Metastatic RCC Diagnosis	Survival Since NSCLC Diagnosis	Decceased
1	M	68	Yes	ccRCC Stage III Gr 2	Squamous Stage I	lung, mediastinal lymph nodes	30 months	Temsirolimus	Stereotactic Radiation	Complete Response	38 months	8 months	No
2	M	61	Yes	ccRCC Stage IV Gr 3	Adeno Stage I	lung, mediastinal lymph nodes, axillary gland	24 months	Surgery, Everolimus	Lobectomy	Complete Response	47 months	23 months	No
3	M	67	No	ccRCC Stage III Gr 2	Adeno Stage IV	lung, liver, pancreas,	15 months	Pazopanib, Nivolumab	Carboplatin/Pemetrexed, Nivolumab	Progression	19 months	7 months	Yes