Metastatic Renal Cell Carcinoma Invading the Pulmonary Vein and Left Atrium: An Extremely Rare Occurrence Treated with Temsirolimus

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Abstract

Metastatic renal cell carcinoma involving the left atrium and pulmonary vein is a very rare entity and has only been reported 4 times in the literature to our knowledge. This has traditionally been managed surgically but we report our experience with mammalian target of rapamycin (mTOR) inhibitor therapy—temsirolimus. The treatment resulted in significant regression of the tumor but more importantly, dramatically improved patient's symptoms.

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Introduction

Most cases of cardiac metastasis from renal cell carcinoma (RCC) involve the vena cava or right atrium.[1] Left heart metastases are relatively uncommon, and involvement of the pulmonary vein is an extremely rare and challenging scenario with only four cases reported to date.[1] All the previously reported cases were treated with surgical resection of the intra-atrial mass. Surprisingly, there is paucity of documented reports of using mammalian target of rapamycin (mTOR) inhibitors in cardiac metastases from RCC. We report a case in which clear cell RCC invaded the left atrium via the right pulmonary vein and was treated non-surgically with temsirolimus. To our knowledge, this is only the fifth occurrence of its kind and only second time when an experience with mTOR inhibitor has been shared in cardiac metastases from RCC.[1,2] This case demonstrates no obvious involvement of the inferior vena cava. The treatment resulted in significant regression of the intrathoracic disease with dramatic symptomatic relief to the patient.

Case History

A 56-year-old woman came to our clinic with gross hematuria and left flank pain. Computed tomographic (CT) scan showed a large inhomogeneous mass arising from the left kidney for which she underwent open radical nephrectomy. Pathology reports from the specimen confirmed a 9 × 7 × 6.5 cm, grade 4 clear cell RCC contained within the renal capsule. All surgical margins (renal artery, renal vein, ureter, and Gerota fascia) and examined lymph nodes were negative for malignancy. The patient was doing reasonably well for approximately 2 years when a CT scan of the chest showed a left upper lobe mass and a right lower lobe nodular density measuring 17 × 25 mm and 35 × 22 mm, respectively. Results of a CT-guided fine needle biopsy of the left upper lobe mass showed clear cell metastatic RCC and overall findings were suggestive of bilateral pulmonary metastatic disease. There was no evidence of metastatic disease elsewhere in the body. The patient was given 7 cycles of sunitinib resulting in resolution of the right lung metastasis and significant reduction in the size of left lung metastasis. Patient thereafter underwent a successful thoracotomy with left upper lobectomy. At this point, patient was radiographically rendered "no evidence of disease." The patient had a stable course for approximately a year, at which time she reported acute onset dyspnea on exertion. A chest CT scan showed right hilar lymphadenopathy, tumor in the right inferior pulmonary vein, and lobulated tumor thrombus in the left atrium (**Figure 1**). After several multidisciplinary discussions, it was concluded that the metastases were not amenable to surgery, and that radiation could cause catastrophic pulmonary vein rupture. Thus, it was decided to start intravenous temsirolimus therapy at a dose of 25 mg weekly. Patient tolerated the treatment well with minimal adverse effects and after 14 weeks of temsirolimus therapy, CT scan showed significant regression of the intrathoracic disease (**Figure 2**) with relief in symptoms and dramatic improvement in dyspnea. Patient is currently reported to have stable disease at almost 11 months from the diagnosis of cardiac metastasis.

Discussion

Cardiovascular involvement from RCC, although rare and limited to case reports, is a reasonably well-recognized entity. The usual pattern of spread (**Table 1**) involves renal vein (33%), inferior vena cava (5%-15%) and right atrium (1%).[3,4] Right ventricular metastases are relatively uncommon (10-15 cases reported to date), and while metastasis to the left side of the heart is exceedingly rare, involvement of the pulmonary veins has only been reported 4 times.[1,5] Some other unconventional vascular sites include superior vena cava, hepatic-portal system, and the carotid artery.[6-8] Despite such underwhelming numbers,

TABLE 1. Distribution of Cardiovascular Metastases in Renal Cell Carcinoma.

Metastatic Site	Frequency
Renal vein[2,3]	33%
Inferior vena cava[2,3]	5% to15%
Right atrium[2,3]	1%
Right ventricle[4]	~15 cases reported to date
Left atrium and Left ventricle[2,3]	Rare (<10 cases)
Pulmonary veins[1]	4 cases reported to date
Others including superior vena cava, portal vein and carotid artery[5-7]	Exceedingly rare (~1 case each)

it is interesting to note that cardiac metastases were shown to be present in 11% of patients who died of RCC.[9]

Cardiac involvement is presumed to be due to 1 of 2 mechanisms: (1) hematogenous spread from the renal vein to the right side of the heart, or (2) through lymphatic vessels of the thorax that allow for the spread of disease to the myocardium and left pericardium, the latter being associated with poorer prognosis.[9,10] Also, in the great majority of cases, the tumor reaches the heart through a neoplastic thrombus within the inferior vena cava.[3] Cardiac metastases without inferior vena cava involvement is extremely rare but can occur through systemic hematogenous seeding or by direct extension from either mediastinal or lung lesions.[1] In the context of left atrial metastases via pulmonary vein, in 3 of the 4 reported cases the tumor originated from the metastatic lung mass, and in the remaining case, from the mediastinal lymph node.[1] Our case is highly unusual in this regard because the left atrial invasion via pulmonary vein was detected approximately a year after left upper lobectomy with no evidence of a pulmonary lesion on previous surveillance CT scan, which makes hematogenous seeding as the possible mode of spread. Furthermore, left heart metastases tend to be clinically silent and often appear late in the course compared with those on the right side, but in our case it appeared quite abruptly with rapid onset of dyspnea.[11] Two of the four reported patients were asymptomatic at the time of detection of left atrial/pulmonary vein metastases, while the other two experienced syncope and dyspnea.[1]

Surgical metastasectomy using a cardiopulmonary bypass with or without hypothermia remains the generally preferred modality for isolated cardiac and inferior vena cava metastases. Sternotomy is the most commonly used approach, but a thoraco-abdominal incision has also been successfully employed.[12-14] Serial echo-guided percutaneous coil embolization has also been used successfully for surgically inoperable cardiac metastases from RCC.[15] Radiation therapy is avoided in pulmonary venous metastases—not only due to the risk of catastrophic pulmonary vein rupture, but also because RCC is often resistant to radiation therapy. All of the four reported cases with pulmonary vein/left atrial metastases were treated with resection of the left atrial mass accompanied by pneumonectomy, but cardiothoracic surgeons deemed our patient's disease inoperable. Therefore, we opted for a conservative mTOR inhibitor therapy with temsirolimus. The use of targeted therapy has been very rarely reported in cardiac metastasis from RCC. More so, the experience with mTOR inhibitor therapy has only been reported once prior to this case but the treatment response is unclear from that study.[2] Our patient showed decent tolerability to the drug with excellent radiographic and clinical response. Some of the other indications for mTOR inhibitor therapy in RCC are high lactate dehydrogenase level, low hemoglobin, high calcium,

TABLE 2. Reported Cases of Left Atrium and Pulmonary Vein Metastasis in Renal Cell Carcinoma.

	Author	Pt Age/Sex	Presenting symptom	Source of cardiac metastasis	Treatment	Outcome
1	Fogel R	77, male	Dizziness, syncope, dyspnea	Lung metastasis	Atrectomy, pneumonectomy	Died postoperatively
2	Patane J	58, female	Asymptomatic	Lung metastasis	Atrectomy, lobectomy	13 months, no recurrence
3	Miyamoto M	56, male	Syncope	Mediastinal node	Atrectomy, lymphadenectomy	4 months, no recurrence
4	Cochnnec F	42, female	Asymptomatic	Lung metastasis	Atrectomy, lobectomy	8 months, no recurrence
5	Present report	56, female	Dyspnea	Hematogenous or adjacent lymph node	Temsirolimus	11 months, stable disease

poor performance status, >2 sites of metastatic disease and <1 year from diagnosis to start of systemic therapy.[16] These parameters are generally indicative of an aggressive disease process and have also been incorporated in the National Comprehensive Cancer Network (NCCN) guidelines. A few case reports have also described tyrosine kinase inhibitors (TKI) such as pazopanib and sunitinib in both, neoadjuvant (prior to cardiac metastasectomy), and inoperable settings.[17,18] Some potential therapeutic options include other TKI's like axitinib and the newly approved cabozantinib, immunotherapy—such as high dose IL-2 and checkpoint inhibitors—but their utility and safety in inoperable cardiac metastases is not known.

FIGURE 1. Chest CT showing Metastatic RCC Invading the Right Inferior Pulmonary Vein and Lobulated Tumor Thrombus in the Left Atrium.

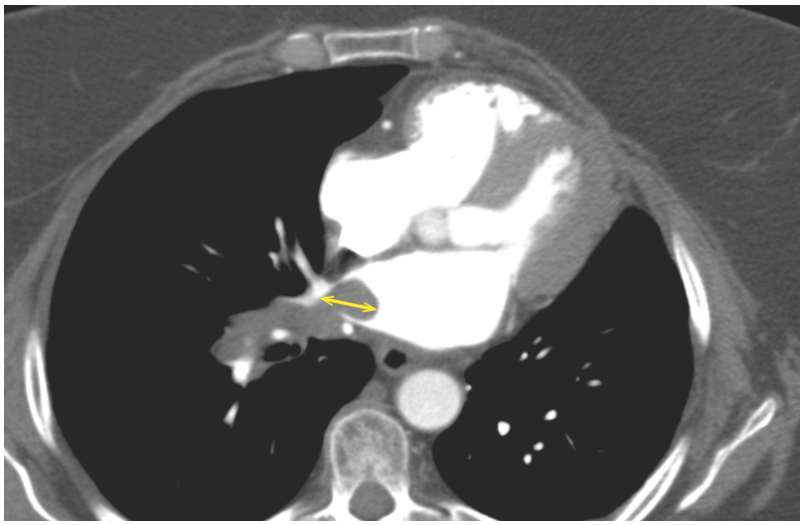
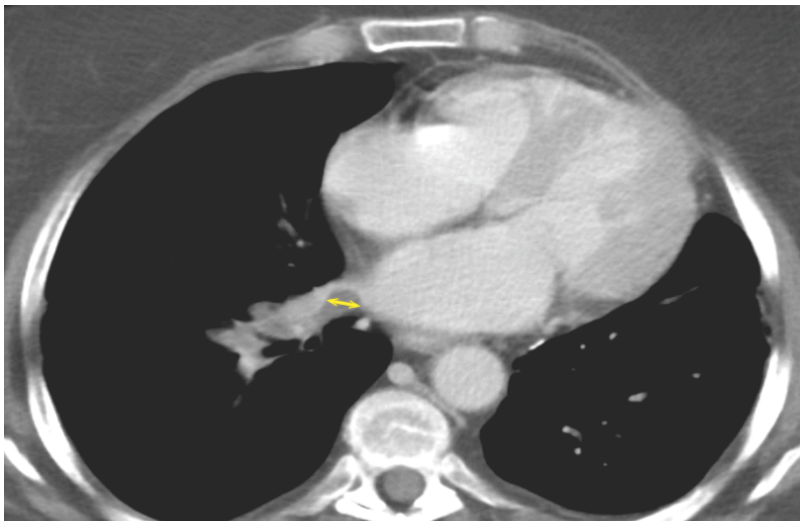


FIGURE 2. CT Scan After 14 Weeks of Temsirolimus Showing Significant Regression of the Left Atrial Mass.



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