

Cardiac metastasis in renal cell carcinoma without vena cava or atrial involvement: an unusual presentation of metastatic disease

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Abstract

Cardiac metastasis in renal cell carcinoma is a very rare entity, with only a few previously reported cases. In this series, we report two cases of ventricular metastases from renal cell carcinoma without vena cava or right atrial involvement. The first case involves an initially isolated inoperable metastasis to the left ventricle, which was treated with systemic targeted therapy with favorable local response. Our second case illustrates a patient with an isolated cardiac metastasis in the interventricular septum with extension into the right ventricle, which has also remained stable in size on systemic targeted therapy. Although anti-angiogenic agents such as tyrosine kinase inhibitors have transformed the treatment of metastatic renal cell carcinoma in recent years, their efficacy and safety in treating patients with metastatic disease in highly vascular organs such as the heart are currently unknown, with no prior reports on this topic. We describe our novel management of these unique cases and discuss the current medical and surgical approaches to treating cardiac metastases from renal cell carcinoma.

Introduction

Primary cardiac tumors are extremely rare and mostly benign.¹ In contrast, metastatic disease of the heart is over twenty times more common.² Cardiac involvement in renal cell carcinoma (RCC) commonly arises from direct tumor thrombus extension into the renal vein, followed by inferior vena cava and/or the right atrium (approximately 5-10% of patients with RCC). The second mechanism of metastasis involves tumor dissemination via hematogenous spread, often leading to widespread organ involvement and has generally been associated with a poor prognosis in the pre-

tyrosine kinase inhibitor era with the use of immunotherapy. Cardiac metastasis in the absence of vena cava extension is exceedingly rare, with only a few cases reported in the literature.³⁻¹¹ In this report we describe two cases of ventricular metastases from RCC in the absence of vena cava or right atrial involvement, explain our novel management, and review the current medical and surgical approaches to treating such cases.

Case Report #1

A 70 year old gentleman underwent left-sided nephrectomy for limited-stage clear cell renal cell carcinoma (ccRCC). More than 20 years later, a chest computed tomography (CT) scan incidentally revealed the presence of a large solid mass in the left ventricle. The patient exhibited no specific signs or symptoms of cardiac involvement and had an excellent performance status. Echocardiogram demonstrated a mass in close proximity to the mitral annulus, with preserved mitral valve function and left ventricular ejection fraction. Cardiac magnetic resonance imaging (MRI) confirmed the finding of a posterior mass measuring 5.5×3.9×34.8 cm in the left ventricle which involved the full thickness of the myocardium from the endocardial surface to the pericardium, causing moderate dyskinesia of the left ventricular wall. Subsequent staging studies confirmed isolated cardiac involvement, with no evidence of metastatic disease elsewhere, and surgical resection of the mass via median sternotomy and institution of cardiopulmonary bypass was planned. However, intraoperatively, the mass was found to be highly vascular and interdigitated with normal myocardium, and was deemed unresectable. An open biopsy was performed, and pathological evaluation was consistent with metastatic clear cell renal cell carcinoma. Given the location of the mass and its involvement of the full thickness of the left ventricle, the potential unforeseen risks of ventricular wall necrosis with either external beam or stereotactic body radiation therapy (SBRT), as well as systemic targeted therapy were discussed with the patient, who elected watchful waiting.

Five months later, he was found to have significant enlargement of the ventricular mass based on repeat imaging studies (7.1×4.4×4.3 cm), though he continued to remain asymptomatic. Treatment with weekly temsirolimus was subsequently initiated and was well tolerated. However, approximately five months later, the patient developed metastatic bone disease and underwent palliative radiation therapy for a symptomatic lytic lesion of the proximal right humerus. Therefore, although the cardiac mass had remained stable on tar-

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geted therapy with temsirolimus, it was felt that a change in systemic therapy was warranted given the rapid progression of bony metastatic disease. The patient was subsequently initiated on treatment with pazopanib at 800 mg daily, which was poorly tolerated with persistent transaminitis despite a decrease in dose to 200 mg daily, so the drug was eventually discontinued 3 months later. Subsequently, therapy was changed to sunitinib which has been well tolerated with evidence of stable disease for the last 7 months. Since initiation of systemic therapy, serial MRIs have shown remarkable stability in the size of the ventricular mass, with gradual development of central necrosis (Figure 1).

Case Report #2

A 64 year old gentleman underwent right-sided nephrectomy for grade 3 stage T3 N0 M0 clear cell renal cell carcinoma with no sarcomatoid features. Four years later, during a routine primary care visit, a new cardiac murmur was discovered. This led to an echocardiogram which showed a 5.3×5.9 cm mass arising from the anterior ventricular septum with extension into the right ventricle (Figure 2A). Multiple biopsy attempts at that time were unsuccessful, but the mass was thought to represent metastatic renal cell carcinoma based on the patient's prior oncological history. He was asymptomatic at the time of diagnosis, and did not exhibit any sign of cardiac dysfunction on physical examination. Further workup revealed a small mass in the head of the pancreas and a 3-cm right gluteal mass, which was

proven by tissue biopsy to be renal cell carcinoma metastasis. The patient was started on systemic therapy with sunitinib. Over two years after the initiation of targeted therapy, the patient was hospitalized for monomorphic ventricular tachycardia. Repeat echocardiogram showed right ventricular outflow tract obstruction and moderate tricuspid valve regurgitation, with no significant change in the size of the right ventricular mass and preserved left ventricular ejection fraction. The patient underwent electrical cardioversion followed by dual chamber ICD (implantable cardioverter-defibrillator) placement. Currently, he is asymptomatic, with stable disease (Figure 2B) and no signs of hemodynamic compromise on a stable dose of sunitinib.

Discussion and Conclusions

Cardiac involvement in metastatic RCC poses a unique therapeutic challenge. Surgical resection can play an important role in the palliation of isolated cardiac metastasis.⁹ For many patients, however, surgical resection is not a viable option as a result of tumor location or medical co-morbidities. Similarly, although conventional and stereotactic radiation therapies are sometimes helpful in treating isolated metastases, their utilization in treating cardiac metastases has been limited. Moreover, when radiation therapy is applied to the treatment of cardiac tumors, it may lead to the development of chronic pericardial disease,^{12,13} and is associated with an increased risk of coronary artery disease.¹⁴

Unlike most other neoplasms, renal cell carcinoma is relatively resistant to classic chemotherapeutic agents, but has demonstrated some sensitivity to immunotherapy. Until recently, interleukin 2 (IL-2) and Interferon- γ have been the only systemic treatment options for patients with metastatic disease. As the biology of renal cell carcinoma became gradually elucidated in recent years, novel applications of targeted therapeutic agents have been developed and offer much improved progression-free survival for this highly vascular malignancy.¹⁵⁻²¹ These treatments include: tyrosine kinase inhibitors (TKIs) such as sunitinib, sorafenib, pazopanib, and axitinib, the monoclonal antibody bevacizumab, as well as mammalian target of rapamycin (mTOR) inhibitors such as temsirolimus and everolimus. Although TKIs show promise in the treatment of renal cell carcinoma, their cardiovascular side effects pose unique challenges in clinical decision making for treating cardiac metastasis. Notable cardiovascular side effects of TKIs include hypertension, arterial and venous thrombosis, cardiac toxicity manifested by a decline in LV ejection fraction,

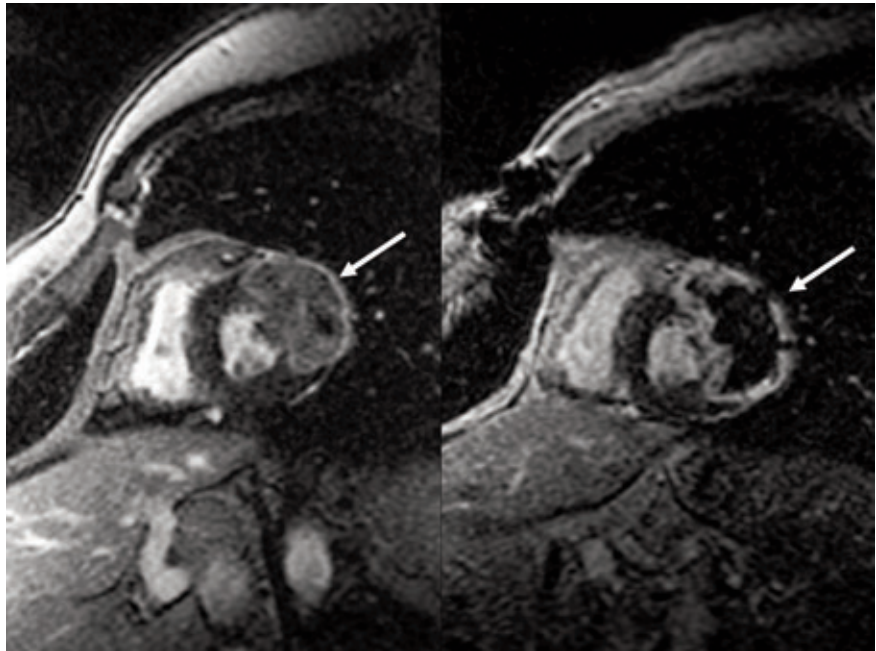


Figure 1. Contrast enhanced cardiac magnetic resonance imaging at the time of initial diagnosis (left) confirmed the finding of a mass measuring 5.5x3.9x4.8 cm in the left ventricle which involved the entire thickness of the myocardium from the endocardial surface to the pericardium. The image in the right panel demonstrates development of central necrosis within the tumor, consistent with response to sunitinib.

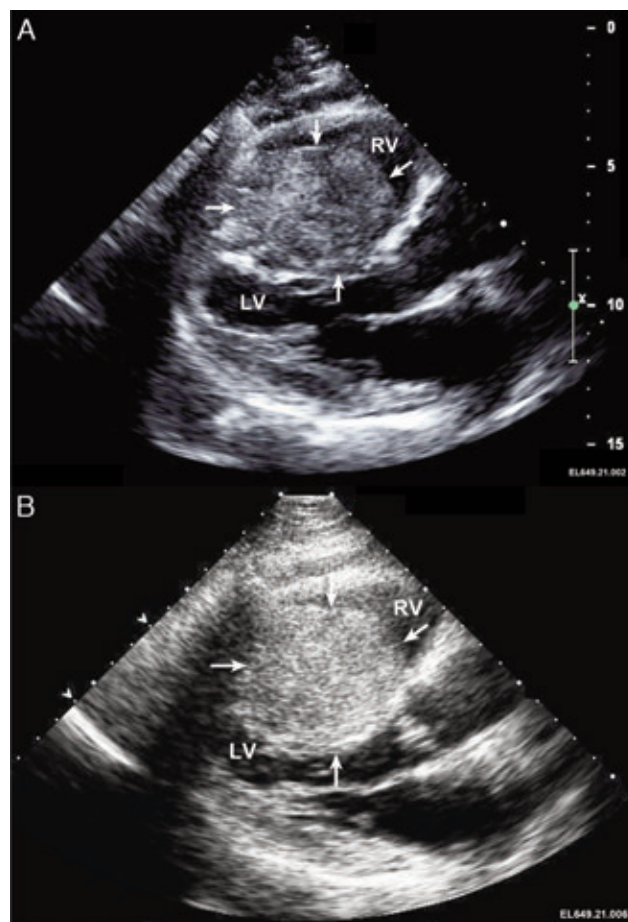


Figure 2. A) Initial echocardiogram showing a 5.3x5.9 cm mass (surrounded by the 4 arrows) arising from the anterior ventricular septum with extension into the right ventricle (RV). B) demonstrates stability in the size of the mass after targeted therapy with sunitinib for 3 years.

heart failure, myocardial ischemia or infarction,²² QT interval prolongation, and hemorrhage. Although TKIs have transformed the treatment of metastatic RCC in recent years,²³ their efficacy and safety in treating patients with metastatic disease in highly vascular organs such as the heart are currently unknown, with no prior reports on this topic. Given the locations of these two patients' tumors and the lack of a surgical solution, after careful review of the risks and benefits associated with anti-angiogenic therapy, we decided to pursue this novel therapeutic approach. Based on our limited data, targeted therapy with sunitinib has been shown to be effective in stabilizing the size of cardiac metastases, and no significant cardiotoxicity has occurred in either patient.

Recently, several studies have documented that after targeted therapy with TKIs,²⁴ metastatic RCC often exhibits decreased attenuation on contrast-enhanced computed tomography, corresponding to pathologic evidence of tumor necrosis. In addition, a recent study by Smith et al reported that the aforementioned radiographic changes are associated with improved clinical outcome.²⁵ We have also noted a similar therapeutic response in our first reported case, as shown in Figure 1. Since the tumor was interdigitated with normal myocardium, the risk of wall perforation associated with treatment-induced necrosis warranted close follow-up with serial imaging studies. We would recommend physicians who attempt this treatment in the future to be mindful of this possibility and monitor their patients closely as we did in these two cases.

Based on our limited observations in these two unique cases, we suggest that despite potential vascular toxicities, targeted anti-angiogenic therapy should be considered as a viable therapeutic alternative to metastasectomy for patients with inoperable cardiac metastatic disease as long as there is no baseline systolic or diastolic dysfunction. During treatment, the patients' cardiac functions need to be closely monitored with frequent office visits and serial echocardiograms. Undoubtedly, long-term follow-up of these two patients will provide valuable information on the efficacy and long-term safety of targeted therapy for patients with cardiac metastases from renal cell carcinoma.

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