

Case Report

Isolated Left Ventricular Metastasis from Renal Cell Carcinoma: Diagnostic and Therapeutic Dilemma

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Keywords

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Abstract

Background: The treatment of metastatic renal cell carcinoma (RCC) has been radically changed by the advent of tyrosine kinase inhibitors (TKIs). However, few reports have described their role in cardiac metastases. We present a case of a left ventricular metastasis from RCC that was managed with pazopanib therapy. **Case Report:** A 74-year-old male with stage I RCC underwent right nephrectomy in 2004 and right lung metastasis resection in 2009. He was well till March 2016, when he presented with chest pain. Cardiac catheterization revealed a highly vascular mass in the apex. Cardiac magnetic resonance imaging revealed a left ventricular mass with full-thickness involvement of the myocardium, and the open cardiac biopsy was consistent with metastatic RCC. The patient was initially treated with pazopanib with response but later developed therapy-related side effects, and the dose was reduced. Due to tumor progression, he is currently on nivolumab instead and is stable. **Conclusion:** RCC with cardiac metastasis poses unique challenges with regard to diagnosis as well as treatment. The use of TKI therapy is associated with cardiotoxicity and has not been adequately studied in cardiac metastasis. Choosing the right treatment for this subgroup of patients continues to pose an ongoing dilemma.

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Background

Renal cell carcinoma (RCC) is among the 10 most frequently diagnosed cancers in men and women in the United States, with more than an estimated 62,000 new cases in 2016 [1]. The prognosis has historically been poor, with current 5-year survival rates of 74% overall, decreasing to 8% among patients with metastatic disease [2]. The most common metastatic sites include the lung, bones, soft tissues, liver, and central nervous system. While cardiac metastases from RCC are unusual, isolated left ventricular metastasis without vena cava involvement is exceedingly rare. Even though the treatment of metastatic RCC has been radically changed by the advent of tyrosine kinase inhibitors (TKIs), few reports have described their role in cardiac metastasis. We present a unique case of a left ventricular metastasis from RCC that was managed with pazopanib therapy, explain our current management, and review existing medical approaches to such cases.

Case Report

A 74-year-old Caucasian man with a history of hypertension and stage I clear cell type renal cell cancer underwent right nephrectomy in 2004. In 2009, he was found to have a right upper lobe lung metastasis and underwent video-assisted thoracoscopic surgery with lung node resection. He had since been doing well without recurrence. In March 2016, he presented with a 1-month history of intermittent chest pressure, predominantly occurring at night times.

On physical examination, his blood pressure was elevated at 183/96 mm Hg with a normal heart rate of 78 bpm. The patient's lungs were clear on auscultation with no abnormalities in the cardiac examination. The abdomen was soft and nontender, and no masses were palpable.

Complete blood count, chemistry panel, thyroid function, and cardiac enzymes were normal. An electrocardiogram showed normal sinus rhythm, with T wave inversions in leads II, III, avF, and V4-V6. A transthoracic echocardiogram followed which revealed reduced ejection fraction of 35% with hypokinesis of the apical segments and a suspicious lesion in the left ventricle. In view of the patient's age and risk factors for coronary artery disease and heart failure, he was scheduled for cardiac catheterization. Cardiac catheterization was performed and did not show significant coronary artery obstructions but revealed an abnormal accumulation of contrast in the apex, suggestive of a highly vascular mass (Fig. 1). To further characterize the mass, cardiac magnetic resonance imaging (MRI) was performed, which confirmed the findings of a left ventricular mass measuring $4.2 \times 3.6 \times 3.1$ cm with full-thickness involvement of the myocardium, causing moderate dyskinesia of the left ventricular wall (Fig. 2, Fig. 3). Open myocardial biopsy was performed, and pathologic evaluation was consistent with metastatic clear cell RCC.

Given the location of the mass and its involvement of the full thickness of the left ventricle, the patient was not felt to be a surgical candidate, and the use of TKI therapy was discussed with the patient. He was initiated on treatment with pazopanib at 800 mg daily, and the size of the tumor decreased to 0.4×0.4 cm in 5 months. The dose of pazopanib was later decreased to 200 mg daily due to therapy-related hypertension and severe fatigue. In January 2017, serial imaging revealed that the tumor size had enlarged to $4.0 \times 3.0 \times 3.0$ cm despite the initial response. Due to tumor progression on pazopanib therapy, he was initiated on treatment with

nivolumab in March 2017. His last serial echocardiogram done in January 2018 showed a stable mass, measuring 4.1 × 3.6 cm with cortical necrosis. He continues to be functional with minimal dyspnea on exertion.

Discussion

Cardiac metastases from RCC in the absence of vena cava extension are extremely rare, and the tumors are often slow growing, with a predilection to present many years after “curative” treatment. Even despite recent advances in the management of metastatic RCC, such as immunotherapies and TKIs, long-term survival of patients with metastatic RCC is limited to months.

There are thought to be 2 general mechanisms of cardiac involvement in RCC. Typically, advanced RCC extends into the renal vein and the inferior vena cava in approximately 5–15% of patients. The second mechanism is via hematogenous spread of the metastasis and has been generally associated with a poor prognosis in the pre-TKI era with the use of immunotherapy. In this present case report, the patient had renal cell cancer likely from hematogenous spread due to isolated involvement of the left ventricle occurring 12 years after initial nephrectomy. Several similar cases have been reported showing late left ventricular metastases occurring even 18–23 years after nephrectomy [3–5].

RCC with cardiac metastasis poses unique challenges with regard to diagnosis as well as treatment. While patients with cardiac metastases are often asymptomatic, they can present with nonspecific symptoms, such as palpitations, chest pain, shortness of breath, and even syncope [6]. Hypertension is the most common cardiac presentation of RCC. Coronary occlusion or compression from tumor masses can lead to myocardial infarction, eventual heart failure, and even death [5]. Pericardial involvement with effusion and cardiac tamponade is the most commonly recognized cause of hemodynamic compromise in these patients [7]. Due to the nonspecific nature of the signs and symptoms, a high index of suspicion is required to make a timely diagnosis of cardiac metastases.

Various diagnostic imaging modalities including echocardiography, computed tomography, MRI, right heart catheterization, and right ventriculography have been used in prior reports [7]. While the ideal diagnostic modality has not been established, Czarnecka et al. [8] have recommended cardiac MRI as the imaging modality of choice in these patients. MRI is felt to be a reliable tool to exclude lipomas, fibromas, and hemangiomas as well as thrombus or lipomatous hypertrophy. Complications of therapy, such as tumor necrosis, extracardiac spread, and pericardial effusion, can be identified with cardiac MRI. In patients on targeted systemic therapy, as in our patient, with risk for tumor necrosis, follow-up cardiac MRIs appear to provide an additional benefit. Serial echocardiograms have also been used as a noninvasive modality to follow cardiac metastases after diagnosis. However, the frequency of surveillance monitoring has not been well established.

With regard to treatment, surgical resection and radiation are usually not feasible, and metastatic RCC is largely resistant to conventional chemotherapy. Prior to the recent advent of angiogenesis inhibitors, cytokine-based therapy, including interferon- α and/or interferon-2, were the mainstay of treatment for advanced RCC. The development of drugs known as receptor TKIs, which include sunitinib, sorafenib, and pazopanib, has created a paradigm shift in the treatment of RCC. These agents have had a remarkable effect on patient outcomes with increased progression-free survival rates [9].

Conversely, the use of TKIs has not been well established in patients with cardiac metastasis from RCC. Although TKIs show promise in the treatment of renal cell cancer, their cardiovascular side effects pose unique challenges. TKIs are associated with cardiotoxicity and have side effects, such as hypertension, heart failure, and necrosis of the myocardium, possibly leading to tamponade and death [10]. The development of heart failure following therapy with sunitinib has been illustrated by Khakoo et al. [11]. Of the 6 patients who developed heart failure, 4 had RCC. Symptomatic heart failure occurred rapidly after initiation of sunitinib (mean onset of 22 days) and was associated with elevations in blood pressure and decline in cardiac function and was not completely reversible even after termination of the therapy. In a landmark trial by Motzer et al. [12] which compared pazopanib therapy to sunitinib in metastatic RCC, patients with underlying cardiac or vascular conditions were excluded from the study. Similarly, in a study by Sternberg et al. [9], comparing pazopanib to placebo in patients with metastatic RCC, patients with a history of cardiac and vascular conditions within 6 months of screening were excluded. In this unique case of cardiac RCC, the ideal treatment modality has yet to be explored. While case reports [13, 14] have shown a promising role of pazopanib therapy in this group of patients, further studies are needed to better elucidate their role.

The primary challenge of metastatic RCC is that complete response to treatment with a single agent is rare and disease progression is an inevitable reality. Prior to 2009, there was no established treatment option for patients who progressed on first-line VEGF-directed therapy. Since then, significant advancement has been made, and the second-line treatment options now include TKIs (axitinib, cabozantinib, and lenvatinib), an anti-PD1 monoclonal antibody (nivolumab), and an mTOR inhibitor (everolimus). Nevertheless, the sequence of treatment remains to be defined as few studies to date have directly compared drug efficacy [15].

Our patient is currently being tried on treatment with nivolumab, a programmed death-1 (PD-1) monoclonal antibody and a recently approved drug for metastatic RCC. Studies show promising results of median progression-free survival of 15.6 months for nivolumab as compared to 11.7 months for everolimus. In patients treated with nivolumab, the median time to response was 3.5 months and the median duration of response was 12 months [16]. Our patient has only been on nivolumab since March 2017 and his tumor has stayed stable.

Conclusion

We have reported one of the few cases of RCC that metastasized to the heart many years after initial nephrectomy. While initial diagnosis was challenging due to the initial presentation with nonspecific symptoms, the more difficult task was to decide on ideal therapy for the patient. In nonresectable cardiac metastasis, as in our patient, the goals of therapy would be to find a balance between slowing the progression of the disease and limiting the toxicity from the treatment. Although TKIs have generally been used for metastatic renal cell cancer, the use in patients with cardiac metastasis should be cautious considering the cardiotoxic effects. Physicians who attempt this treatment in the future need to be aware of the possibility of cardiac wall perforation from treatment-induced necrosis. An alternative treatment in this subgroup of patients has not been defined, and choosing the right treatment for this subgroup of patients continues to pose an ongoing dilemma.

Statement of Ethics

The authors have no ethical conflicts to disclose.

Disclosure Statement

The authors have no conflicts of interest to declare.

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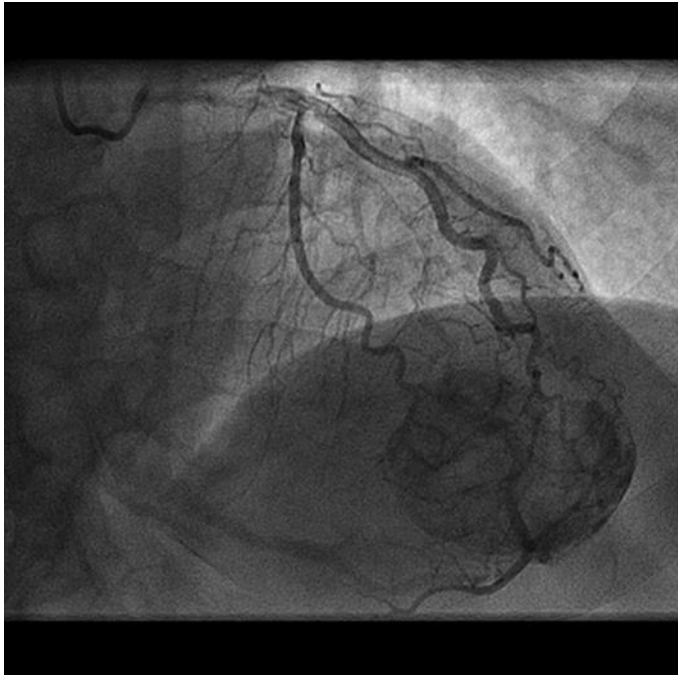


Fig. 1. Cardiac catheterization showing accumulation of contrast in the apex of the heart and a large, vascular, well-circumscribed structure.

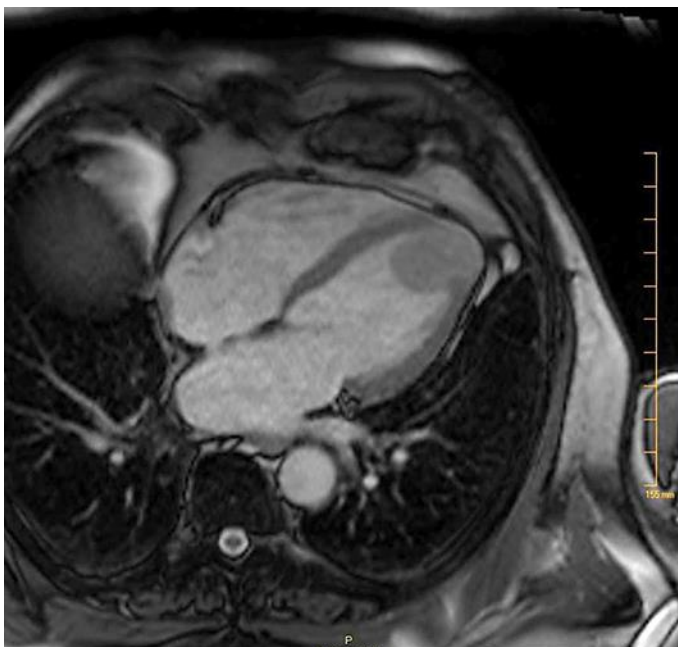


Fig. 2. A mass in the apex of the left ventricle with probable full-thickness involvement of the apical myocardium inferiorly and inferolaterally, measuring 4.2 × 3.6 × 3.1 cm.

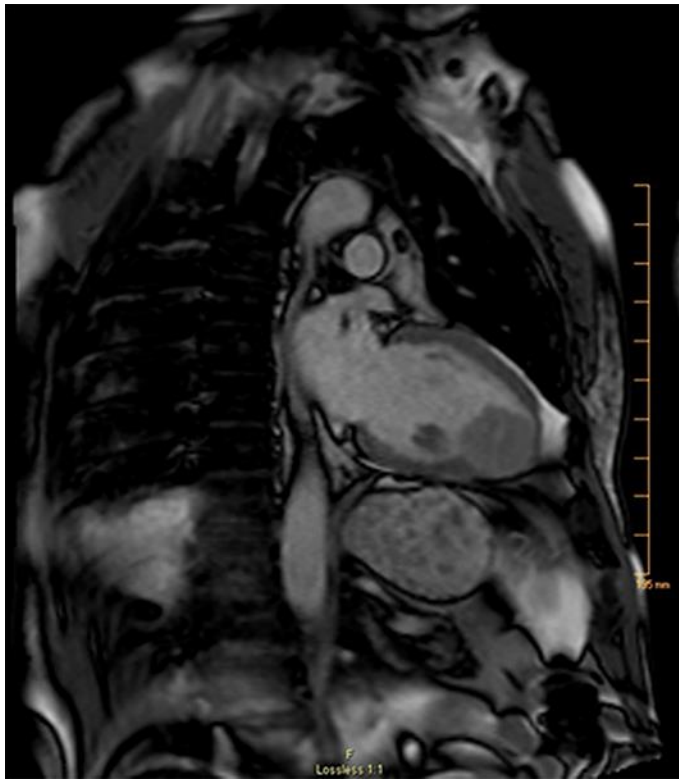


Fig. 3. A mass in the apex of the left ventricle with probable full-thickness involvement of the apical myocardium inferiorly and inferolaterally, measuring 4.2 × 3.6 × 3.1 cm.