Symptomatic cardiac metastasis responding to pazopanib in a patient with renal cell carcinoma

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We report a case of an 82-year-old man with renal cell carcinoma who developed a cardiac metastasis within the interventricular septum. He had been under watchful waiting for indolent metastatic renal cell carcinoma for many years before developing symptoms consistent with heart failure. At this time, a 44 mm interventricular septal mass, consistent with a cardiac metastasis, was identified as the cause of his symptoms. Pazopanib was initiated which led to both a clinical and radiological response.

Key Words: cardiac metastases, renal cell carcinoma, pazopanib

Introduction

Renal cell carcinoma (RCC) accounts for 2%-3% of all adult malignancies and has the worst cancer specific mortality among urologic tumors with median survival of 13 months and 5 year survival rate of 15% for metastatic disease.[1] The most common sites of metastases include lung (75%), bone (20%), liver (18%), cutaneous sites (8%), central nervous system (8%) and soft tissue (6%).[2] Cardiac metastases from RCC are rare.

It is well known that RCC can extend into the renal vein and inferior vena cava (IVC); extension of this tumor thrombus into the right atrium can also occur. Given this type of tumor thrombus extension, the most common RCC associated cardiac metastases involve the right atrium. Metastases to cardiac muscle within other chambers are particularly rare. Regardless of their location, cardiac metastases can result in heart failure. In these patients, it is unknown whether small molecule tyrosine kinase inhibitors such as sunitinib or pazopanib can be given safely, particularly in the context of their well-described cardiotoxicity profile.

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In this case report, we describe an 82-year-old patient with known metastatic RCC, who developed heart failure secondary to an interventricular septal cardiac metastasis. We also detail his clinical and radiological response to pazopanib.

Case report

In 1991, a 59-year-old gentleman presented to his local doctor with hematuria. He was investigated and found to have a left renal mass. He went on to have a left radical nephrectomy which demonstrated a 50 mm, T1b, poorly differentiated, clear cell RCC with no vascular invasion. Staging demonstrated no nodal or metastatic disease. In 2006, 15 years following his initial diagnosis, our patient was incidentally found to have a 60 mm right adrenal mass consistent with a metastasis and went on to have a right radical adrenalectomy which demonstrated poorly differentiated clear cell RCC. Then, in 2010, during active surveillance, a routine CT scan detected a heterogeneous necrotic mass in the head of the pancreas, measuring 46 mm in maximal diameter. This was deemed unresectable. An ultrasound guided fine needle aspiration biopsy was performed and demonstrated clear cell RCC. At this time, the patient remained asymptomatic and his ECOG performance status was 0. He entered a watchful waiting program, consisting of regular CT scans and a plan to initiate systemic therapy when symptomatic.

In the subsequent 4 years, our patient remained on watchful waiting. His pancreatic metastasis continued to increase in size slowly. His lung nodules remained stable. Given he remained asymptomatic he was not offered systemic therapy.

In February 2014, our patient, now 82 years old, presented to the emergency department with central chest pain and exertional dyspnea after only a few steps. He was found to have evidence of biventricular heart failure, with peripheral edema, a raised jugular venous pulse and pulmonary edema. He improved rapidly with diuresis. A thorough cardiac workup excluded an ischemic cause for his symptoms. In particular, cardiac enzymes were normal and an electrocardiogram only revealed a pre-existing right bundle branch block. During his admission, review of a recent surveillance staging CT revealed a cardiac mass within the interventricular septum, not previously identified, that was suspicious for metastasis. This mass extended into the inferior wall of the left ventricle, protruded into the right ventricle which was significantly compressed and extended superiorly causing outflow narrowing at the pulmonary valve and compression of the aortic valve from its anterior margin. The mass measured 44 mm wide on axial images, Figure 1. This scan was performed several weeks prior to his emergency presentation and prior to the development of cardiac failure, subsequently the scan did not demonstrate any radiological evidence of heart failure. On the same CT scan, the known pancreatic mass had also continued to increase in size, now measuring 66 mm in maximal diameter.

Given the difficult nature of obtaining a specimen from the cardiac mass for histological assessment, together with the high likelihood that it represented a metastasis, the patient was presumed to have an RCC cardiac metastasis. Although, the patient's acute onset chest pain and dyspnea improved with diuresis, on discharge, he continued to have exertional dyspnea over 10 meters. In the context of these persisting cancer-related symptoms, caused by the cardiac metastasis, in March 2014, the patient was started on pazopanib 800 mg daily as systemic therapy, with the hope that a response to treatment would improve his symptoms.

Within 3 months of starting pazopanib, our patient gained an excellent clinical response; he no longer experienced exertional dyspnea or any other symptoms of heart failure. Additionally, our patient tolerated the treatment well, with no significant toxicity. A restaging CT scan in June 2014 confirmed a radiological response, with a 32% reduction in the size of the cardiac metastasis, now measuring 30 mm wide on axial images, Figure 2. This scan also demonstrated evidence of heart failure, with cardiomegaly and a small pericardial effusion; however, he remained asymptomatic. Additionally, the scan demonstrated

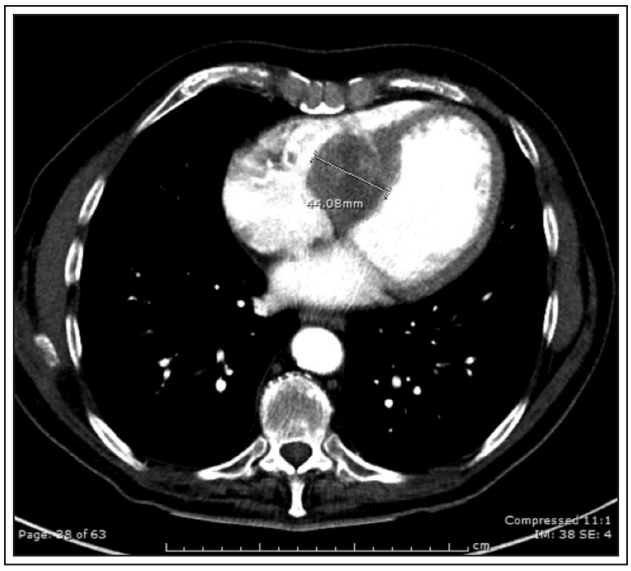

Figure 1. Computed tomography image of interventricular septal cardiac metastasis at baseline, prior to pazopanib therapy.

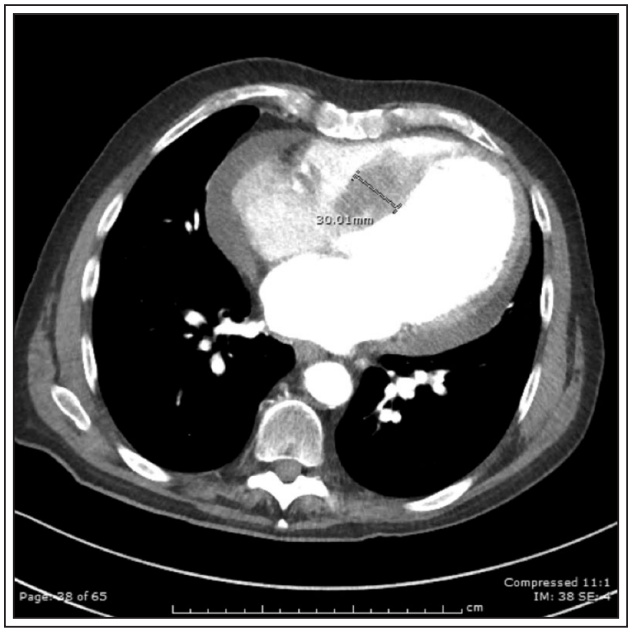

Figure 2. Computed tomography image of interventricular septal cardiac metastasis following 3 months of pazopanib therapy.

a radiological response in the head of pancreas mass, with an 18% reduction in size, now measuring 54 mm on axial imaging. An echocardiogram was also performed at this time and demonstrated a severely thickened interventricular septum causing only minor impingement into the right ventricle and no longer compressing the aortic valve, as previously seen on CT.

At the time of writing, in January 2015, the patient remained on pazopanib, tolerating treatment well with ongoing clinical and radiological response. The most recent restaging CT scan in January 2015 demonstrated the cardiac metastasis to be stable, measuring 32 mm wide on axial imaging.

Discussion

Although extension of tumor thrombus into the right atrium via the IVC has been well described for metastatic RCC, cardiac metastases are extremely rare and present a unique therapeutic challenge. A post mortem series of 11,432 autopsies revealed 266 cases of neoplasms involving the heart with just three cases originating from RCC.[3] Additionally, there have been only two reported cases of RCC cardiac metastases involving the interventricular septum.[4,5] Our case is unique. Not only does our patient have a cardiac metastasis involving the interventricular septum in the absence of tumor thrombus extending into the IVC, but we have also described his clinical and radiological response to pazopanib.

Cardiac metastases have been managed surgically in some patients. For carefully selected patients resection of cardiac metastasis has led to symptom control, improvement in quality of life and prolonged survival. However, for many patients, surgical resection is not feasible. An alternative is radiotherapy, however, its use in treating cardiac metastasis has been limited due to the potential direct cardiac toxicity.[6] In the absence of a surgical or radiotherapy approach, systemic therapy remains the only option for cardiac metastases.

In recent years, improved understanding of RCC tumor biology, in particular, the importance of the Von Hippel-Lindau (VHL) gene in driving tumor angiogenesis, led to the successful development of several new therapies for metastatic RCC. Over the last decade, the introduction of sunitinib, sorafenib, temsirolimus, everolimus, bevacizumab, pazopanib and axitinib has been associated with significant improvements in survival for patients with metastatic RCC.

While providing significant benefits to metastatic RCC patients, these novel targeted therapies also have significant toxicity. Of particular interest to our case, is the potential for cardiotoxicity, in particular heart failure. A meta-analysis of 6935 patients treated with sunitinib, found that 4.1% developed heart failure. Other studies have suggested a rate as high as 33.8%.[7] The mechanism remains unclear for many of these tyrosine kinase inhibitors, but is likely to be a combination of "on-target" toxicity, related to their anti-angiogenic effect, and "off-target" toxicity related to inhibition of other kinases.

Prior to prescribing pazopanib for our patient, we had significant concerns over the potential for worsening heart failure. However, given the patient's heart failure was directly related to a cardiac metastasis, the decision was made to start systemic therapy.

To the best of our knowledge, four previously published case reports have described patients with RCC and cardiac metastases treated with tyrosine kinase inhibitors.[5,8,9] Our case is unique, in that it is the only report of a patient who presented with symptoms consistent with heart failure caused by a cardiac metastasis. Additionally, our case is the only report to describe clinical improvement of heart failure following a favorable response to initiation of systemic therapy.

Our case report demonstrates that there is a potential role for small molecular tyrosine kinase inhibitors in treating patients with metastatic RCC who have symptomatic heart failure resulting from cardiac metastases. □

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