An unusual site of metastasis from gastrointestinal stromal tumor

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Abstract

Gastrointestinal stromal tumors are mesenchymal tumors of the gastrointestinal tract. They commonly metastasize within the abdominal cavity, particularly to the liver. Less commonly, metastases can be found in the lung or bone. This report describes the first two cases of metastasis to the left ventricle in patients with advanced gastrointestinal stromal tumor.

Introduction

Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal tumors of the gastrointestinal tract, arising predominantly in the stomach (60-70%), small intestine (20-25%), colon and rectum (5%), or esophagus (<5%).[1] Approximately 90% of GISTs stain positively for the receptor tyrosine kinase, KIT (or CD117). Eighty-five percent of tumors contain mutations in *KIT* and 5% in *PDGFRA*.[2] GISTs most commonly metastasize to the liver and abdominal cavity.[3] Extra-abdominal metastases are extremely rare, with pulmonary and bone metastases being the most frequent sites. We report here the first two cases of metastatic GIST to the left ventricle.

Case Reports

Case #1

A 48-year-old healthy male presented with abdominal pain, nausea, vomiting, diarrhea, and a palpable abdominal mass. A computer tomography (CT) scan revealed a large right lower quadrant mass with liver lesions. He underwent resection of a 21×20×13 cm mass arising on the small intestine, a 5 cm right colonic mass, as well as the small bowel mesentery and peritoneum diffusely infiltrated by multiple nodular lesions. Morphological and immunocytochemical features of the tumor were consistent with GIST.

After the surgical resection, imatinib therapy was administered at a dose of 400 mg daily, initially complicated by transient transaminitis. Eighteen months later, he was found to have progressive liver metastases and his dose of imatinib was increased to 600 mg daily, followed by surgical debulking of three liver lesions. Six months later, his daily dose was increased to 800 mg. During this period he also underwent two courses of radio frequency ablation of several liver lesions. The patient was noted to have additional liver metastases and pulmonary nodules and began therapy with sunitinib. He was started on a clinical trial of nilotinib for progressive disease six months later.

On restaging studies following six weeks of therapy, a CT scan of the chest, abdomen, and pelvis revealed stable pulmonary metastases and an increase in size of the multiple liver metastases, minimally less than 20% progression from baseline. It also demonstrated a 2.5×3.5 cm hypo-attenuating focus along the inferior wall of the left ventricle (Figure 1), which was found to be metabolically active on positron emission tomography (PET) imaging (Figure 2). Echocardiography was performed to determine if the lesion was metastatic disease or a thrombus. The examination revealed normal left ventricular size and function and normal left ventricular wall thickness. The study confirmed the presence of a moderate-sized mass attached to the inferior and apical walls of the ventricle, consistent with metastatic GIST.

Case #2

A 61-year-old male with a history of type II diabetes, benign prostatic hypertrophy, coronary artery disease, and hypertension, and a family history notable for three brothers with stomach malignancies, developed abdominal pain that was not relieved by antacids or proton pump inhibitors. He presented to his local emergency room for these complaints two months later with complaints of abdominal pain. A CT scan demonstrated a 15 cm small intestine mass that was abutting on the bladder. He underwent resection of an approximately 15.0 cm intra-abdominal mass with partial cystectomy. The tumor was diagnosed as a gastrointestinal leiomyosarcoma and no additional therapy was given at that time. Five years later, the patient noticed abdominal fullness. He was found to have a local recurrence, which was resected.

A second recurrence was diagnosed two years later. At this time, the patient's pathology was reviewed. His pathologic diagnosis was changed to GIST, a mixed spindle- and epithelioid-cell neoplasm with a diffuse intermediate positive staining for c-KIT and diffusely strongly positive staining for SMA and vimentin. He was treated with imatinib, 400 mg daily, achieving stable disease. He had a surgical resection of the recurrent GIST that same year. Three years later, while on imatinib, he developed back pain and a repeat CT was performed. He was found to have multiple pelvic metastases that occluded his left ureter. An echocardiogram performed in anticipation of sunitinib therapy revealed a 5×2.5 cm left ventricular wall mass. A magnetic resonance image (MRI) of the heart (Figure 3) revealed a lesion that appeared to be attached to the lateral mid left ventricular wall, separate from the valves, measuring 3.8×3.3×3.9 cm, which was most likely a metastatic focus. The patient has been started on sunitinib, 37.5 mg daily; complicated by a deep venous thrombosis, pulmonary embolism, and atrial fibrillation.

Discussion

The term GIST was first coined by Mazur and Clark in 1983 to include a heterogeneous group of non-epithelial neoplasms of the gastrointestinal tract.[4] Surgery has been the mainstay of therapy with limited benefit from radiation and cytotoxic chemotherapy.[5] Despite successful surgical therapy, GISTs exhibit a high risk for metastatic relapse, predominantly local recurrences, liver, and peritoneal metastases. The median disease-specific survival in

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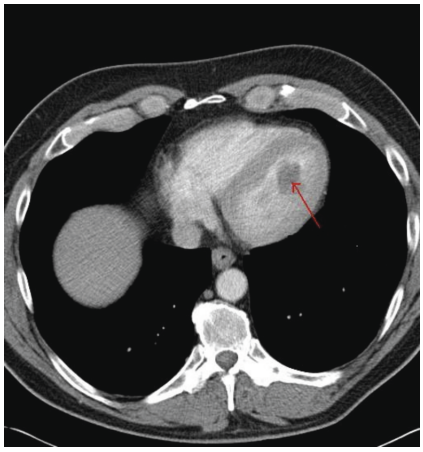

Figure 1. Computer tomography image with red arrow delineating the left ventricular mass.

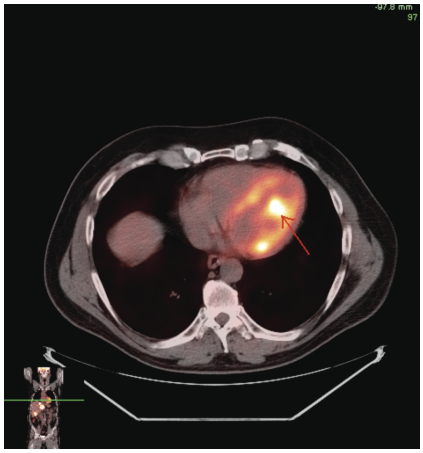

Figure 2. A positron emission tomography image showing a metabolically active left ventricular mass (red arrow).

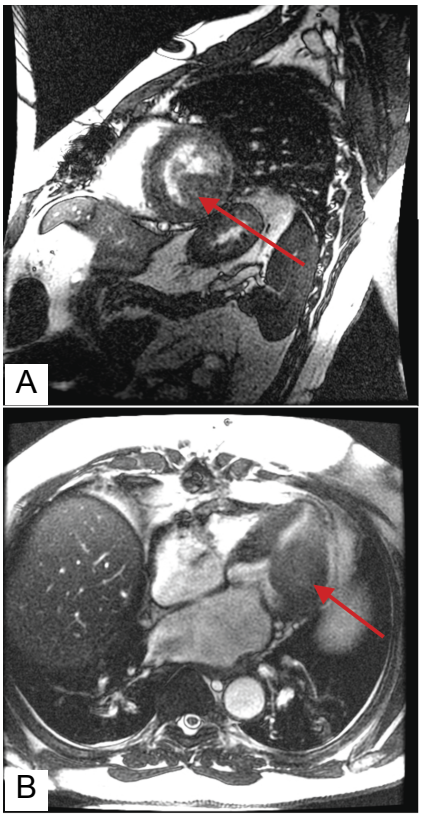

Figure 3. A FIESTA magnetic resonance image showing: (A) short axis oblique view, and (B) four-chamber oblique view, with red arrows pointing to the left ventricular wall mass.

patients with recurrent and metastatic GIST has been reported to be 12 and 19 months, respectively.[6]

In 1998, Hirota *et al.*[7] identified gain-of-function mutations of the *KIT* proto-oncogene in the majority of GISTs. Similar activating mutations have been identified in *PDGFRA*.[8] Imatinib was the first targeted agent studied in advanced GISTs. It inhibits several receptor tyrosine kinases including KIT, PDGFRA, and PDGFRB. Data from a pooled analysis of the phase III trials comparing 400 mg/day and 800 mg/day imatinib doses indicated no statistically significant differences in median progression-free survival or overall survival, except for those whose tumors carried an exon 9 mutation, in which there was a benefit in progression-free survival at the higher dose.[9] In the advanced and metastatic settings, imatinib at an initial dose of 400 mg/day is standard first-line therapy, with dose escalation up to 800 mg/day in those with mutations in exon 9 or disease progression at the lower dose.[10]

Sunitinib inhibits multiple receptor tyrosine kinases including KIT, PDGFRA and PDGFRB, VEGFR-1, VEGFR-2 and VEGFR-3, FMS-like tyrosine kinase-3 receptor, the receptor for macrophage colony-stimulating factor, and glial cell line-derived neurotrophic factor receptor.[11] A completed phase III study randomized patients to placebo or sunitinib in a double-blinded trial in advanced GIST resistant to 800 mg/day imatinib or intolerant of imatinib, with crossover to sunitinib at the time of progression for patients on the placebo.[12] At the initial interim analysis, median time to progression for the placebo and the sunitinib groups were significantly different (1.5 vs. 6 months, respectively), leading to termination of the study and crossover of patients on the placebo. There was an 8% partial response in the sunitinib arm compared to none in the placebo group. Additional agents are being tested for treatment in the third line setting. Nilotinib, the investigational agent in case #1, is a second generation aminopyrimidine inhibitor of KIT, PDGFR, and BCR-ABL. A phase I trial of nilotinib in GIST has demonstrated safety and clinical benefit in patients with imatinib and sunitinib refractory disease.[13]

Targeted therapies have dramatically improved the outcomes in GIST. Patients are living longer with metastatic disease. With longer survival and the use of palliative therapies, new sites of metastases are being reported. One case report describes brain metastases following an initial presentation of a jejunal GIST with liver metastases.[14] Interestingly, this patient had received only surgery and cytoreductive chemotherapy, and had not received tyrosine kinase inhibitor therapy prior to this diagnosis. The patient was palliated successfully with imatinib for 15 months before further progression. There is also a case report of a testicular metastasis.[15] Lastly, lymph node metastases are said to be uncommon at primary disease presentation but, as was seen in this patient, can be observed in patients with metastatic disease. Our report is of interest because extra-abdominal metastases are uncommon. This report describes the first documented cases of metastatic GIST to the heart.

In conclusion, the occurrence of a cardiac metastasis, in our opinion, is not the result of the therapy that these patients received but rather of prolonged metastatic disease palliated by multiple modalities. The availability of imatinib, sunitinib, and several other promising investigational therapies, either alone or in combination, is leading to increasingly prolonged survival and "new" sites of disease.

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