Case Report

Unusual metastases of gastrointestinal stromal tumor and genotypic correlates: Case report and review of the literature

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Introduction

Gastrointestinal stromal tumors (GISTs) are defined as mesenchymal tumors of the gastrointestinal tract and are characterized by positive CD117 staining, and in most cases positive CD34 staining, with compatible gross features and microscopic findings of a highly cellular mesenchymal tumor of the gastrointestinal tract composed of spindle cells, epithelioid cells or a combination of both (1). They are usually derived from a mutation of the KIT (CD117) or PDGFRA (platelet derived growth factor receptor alpha) gene. Distinguishing GIST from other mesenchymal derived tumors was historically a challenge, since both can arise from the interstitial cells of Cajal, or GI pacemaker cells that form the interface between the autonomic innervation and smooth muscle of the bowel wall (2). The distinction of GISTs based on molecular etiology was described by Hirota et al in 1998, with discovery of a mutation in c-KIT encoding a pro-oncogenic receptor tyrosine kinase (KIT) (3).

It is estimated that 4500 to 6000 new cases of GIST are diagnosed in the United States annually and most occur in the stomach (50%-70%) or small intestine (20%-30%) (4). GISTs are often asymptomatic and discovered incidentally during surgery, endoscopic procedures, or imaging studies. However, the clinical presentation of some GISTs may include overt GI bleeding, abdominal mass, abdominal pain, or bowel obstruction and acute abdomen (2). The most common metastatic sites of gastrointestinal stromal tumors are the liver (65%) and peritoneum (21%); GISTs rarely metastasize to lymph nodes (6%), bone (6%), lung (2%) (2,5), and soft tissue (less than 1%) (6,7). We report the case of a female diagnosed with GIST with subsequent metastases to the liver, peritoneum, lung, bone, and soft tissue.

Case presentation

A 57 year-old Caucasian female, with history of hypertension and diabetes mellitus, presented to an emergency department (ED) in March 2003, with complaints of acute onset of abdominal pain and three month history of fatigue. Her evaluation revealed anemia with hemoglobin of 6.8 gm/dL, and a small bowel obstruction by CT imaging of the abdomen/pelvis (Fig 1). She underwent a small bowel mass resection. Pathology confirmed a gastrointestinal stromal tumor with a 9 cm primary tumor in the jejunum. Immunohistochemistry revealed spindle cells positive for CD117 (Fig 2) and CD34, negative for S-100 protein, cytokeratin, and smooth muscle myosin. Mitotic activity was low (<5/50 per HPF).

The patient was clinically stable and followed by serial imaging until May 2004, when she complained of right upper quadrant abdominal pain and a CT scan of the abdomen revealed liver metastases. The patient began treatment with oral imatinib mesylate (Gleevac) at a dose of 400 mg/day, and a partial response was achieved for two

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years. The patient then experienced recurrence of right upper quadrant pain and a CT scan demonstrated increase in the size of liver metastases and a new pleural effusion. Subsequent treatment was initiated with oral sunitinib malate at a dose of 50 mg/day, on a schedule of 28 days on and 14 days off. The patient experienced significant side effects including fatigue, severe mouth soreness, decreased appetite, and hand-foot syndrome, necessitating dose reduction to oral sunitinib malate at a dose of 37.5 mg/day after three cycles on the initial dosage. Stable disease was achieved for approximately twelve months while on oral sunitinib.

In April 2007, she had progression of disease in the form of a pathological fracture of the left humerus. Biopsy of the left humerus revealed a spindle cell sarcoma morphologically consistent with GIST metastasis, however immunohistochemical stains were negative for CD117 (c-KIT), CD34, and bcl-2. Sunitinib was discontinued preoperatively, and the patient underwent reconstruction of the left distal humerus. A CT of the abdomen and pelvis in May 2007 showed dramatic progression of liver metastases (Fig 3). Given the progression of disease while being off sunitinib and in the absence of other standard of care treatment, she was restarted on oral sunitinib malate at a dose of 37.5 mg/day, on a schedule of 28 days on and 14 days off. In August 2007, she developed hard nodules in the subcutaneous area of the left upper extremity, concerning for tumor recurrence. CT scan of the left humerus revealed multiple soft tissue nodules scattered throughout the humerus (Fig 4). She continued sunitinib as systemic therapy and began local radiation therapy of the left humerus for palliation.

In October 2007, the patient was hospitalized for dyspnea, ascites, and lower extremity edema. Imaging showed further metastases to the peritoneum and lungs and bilateral pleural effusions (Fig 5). Despite two thoracenteses and pleurodesis, she had progressive symptoms and worsening lung nodules. Her respiratory failure was rapidly progressive and she died in October 2007, approximately 55 months after her initial diagnosis.

Due to unusual sites of metastases, a limited autopsy of the liver, lung and left arm tissue was performed after written consent from her power of attorney. The lung and liver metastatic lesions were morphologically consistent with GIST, and immunohistochemical stains were positive for CD117 (c-KIT). Tumor cells from the left arm subcutaneous nodule were morphologically suggestive of GIST but negative for CD117 by immunohistochemical staining. Molecular analysis demonstrated an in-frame deletion of 74450-74455 (6bp), or del559V-560V (or codons 559/560) in exon 11 of the KIT gene in sequences from metastases of the right lung, left lung, liver, and left arm subcutaneous nodule. No mutation in exon 18 of the PDGFRA gene was identified in these metastases.

Review of the literature

Outside of a retrospective analysis conducted by Schuler et al (5), which reported that seventeen out of 307 patients with GIST had bone metastases, there are only a few reported cases in the literature of patients with GIST metastases to the bone, lung, or both (Table 1). Kaku et al (8) described a case of a 68 year-old woman with intracranial metastasis occurring two years after surgical

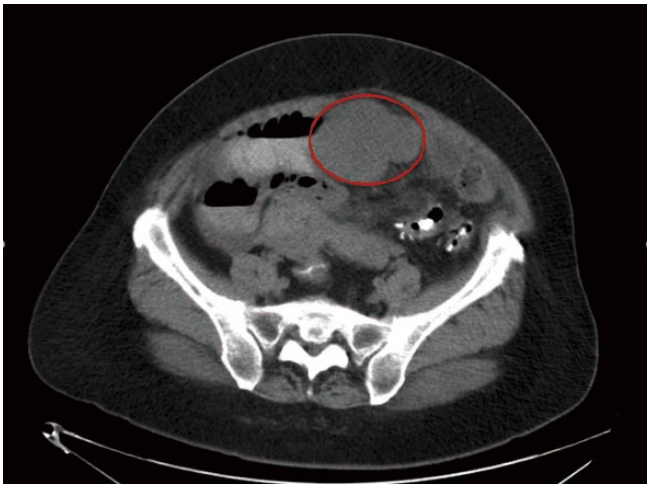

Figure 1. Gastrointestinal stromal tumor of the jejunum with associated small bowel obstruction (red oval marks approximate tumor boundary).

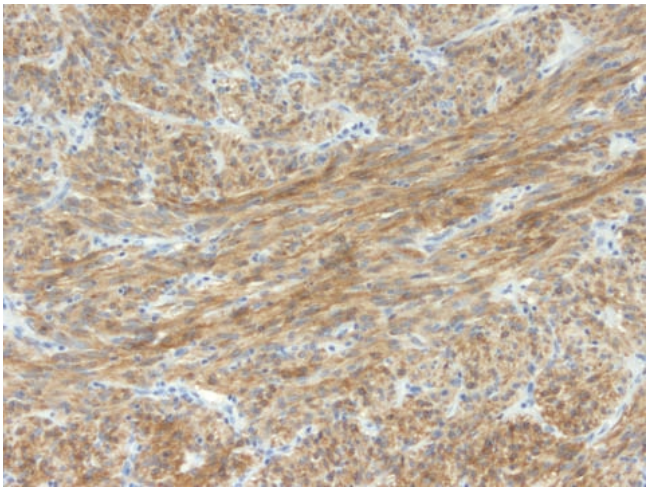

Figure 2. Gastrointestinal stromal tumor: Low-power view of immunohistochemistry showing spindle cells diffusely positive for CD117.

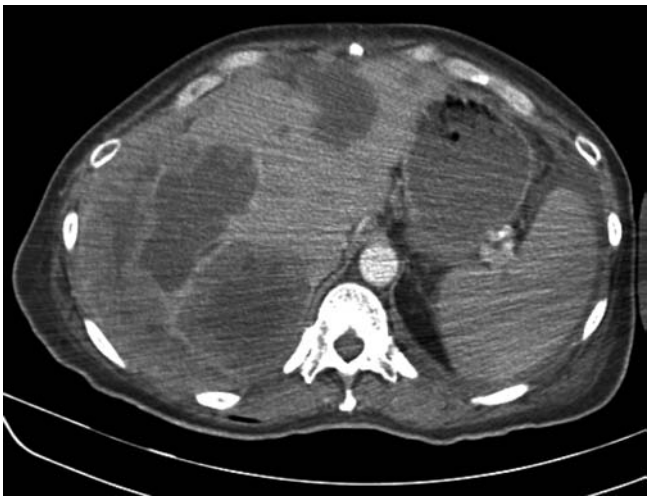

Figure 3. Imaging of the abdomen by CT showing multiple large liver metastases.

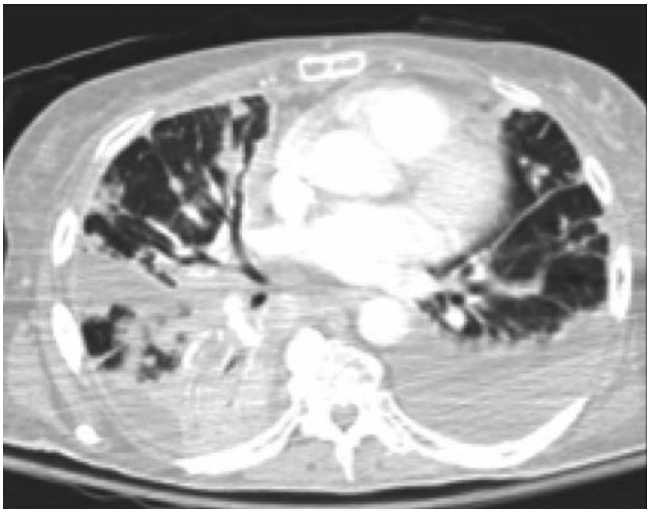

Figure 5. Chest CT image demonstrating multiple pulmonary nodules, compressive atelectasis and associated bilateral pleural effusions.

resection of a GIST tumor of the sacrum. She subsequently developed metastatic tumor involving the lumbar spine and ureter. The intracranial metastasis was resected by right parietal craniotomy and was c-KIT positive by immunohistochemistry. Biopsy or surgery was not performed on the lumbar spine and ureter lesions. A 37 year-old man with primary GIST of the liver metastatic to the lung is described by DeChiara et al (9). The primary tumor was initially diagnosed as a high grade sarcoma, but after further immunohistochemical study, the liver tumor cells stained positively for c-KIT and the tumor was diagnosed as

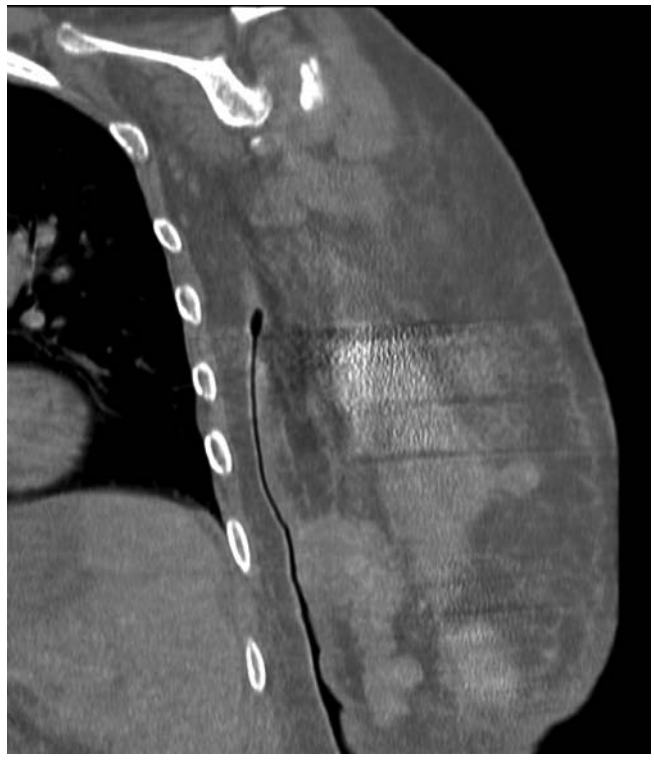

Figure 4. CT imaging of left humerus in the coronal plane showing multiple metastatic soft tissue nodules.

GIST. Fourteen months after this diagnosis, the patient was found to have lung metastases by CT scan, and confirmed by PET. While pathology and immunohistochemistry were not reported on the lung metastases, it was reported that the pulmonary lesions disappeared completely with oral imatinib treatment, suggesting a similar molecular basis of these lesions. Miyake et al (10), and Inage et al (11), described patients with multiple sites of metastases, with both patients having lung metastases. Ishikawa et al (12) reported a patient with liver and bone metastases, in the form of a lumbar vertebral lesion. With the exception of our report, mutational studies of KIT and PDGFRA genes were not reported in these five other cases (8-12).

Even more rare than metastases to bone and lung, metastases of GIST to subcutaneous tissue are reported in less than 1% of cases (6,7). In a series of patients with stomach GIST, five out of 1765 patients (0.04%) developed skin or soft tissue metastases (6). No patients were reported to have soft tissue or skin metastases in a series of 906 patients with small intestine GIST (7). Prior to our reported case, the literature includes six case reports (13-18) describing ten patients with cutaneous metastases as a late complication of GIST. The first reported case (13) described a 49 year-old male with multiple skin and

Table 1. Case Reports describing GIST metastasis to bone, lung, or both.

Author	Age (yr), sex	Location of metastasis	Immunohistochemistry
Kaku S (6)	68 female	Lumbar spine, intracranial (brain), ureter	Intracranial: CD117 and CD34 positive
De Chiara A (7)	37 male	Lung	Primary tumor (liver): CD117 positive, No immunohistochemistry reported on lung metastases
Miyake M (8)	45 female	Liver, lung, peritoneal	Primary tumor (jejenum): CD117 positive
Inage Y (9)	70 male	Lung, intracranial (left occipital)	Histology and immunohistochemistry showed that both sites were metastases of GIST
Ishikawa A (10)	58 male	Liver, L5 lumbar vertebra	Not reported in abstract
Our case	59 female	Liver, lung, peritoneal, bone	Liver, Lung metastases: positive for CD117, Bone metastases: negative for CD117

subcutaneous metastases to the scalp, anterior jaw, left thigh, and groin, along with liver and splenic metastases. This report did not include description of microscopic, immunohistochemical and molecular features. The patient was treated with gemcitabine and thalidomide, experienced a minimal response and was then lost to follow up. Anagnostoulis et al (14) reported a 69 year-old female who presented with synchronous gastric GIST and a subcutaneous paraumbilical metastasis, proven by histology and immunohistochemistry to be consistent with GIST. She died four days postoperatively after gastrectomy and resection of subcutaneous metastasis. Other reports described three patients with subcutaneous metastases in the parietal bone region (15), gluteal region (biopsy proven and immunohistochemistry positive for CD117) (16), and right upper arm (biopsy proven, immunohistochemistry positive for CD117) (17) respectively.

Outside of our article, the only other literature to report subcutaneous metastasis of GIST and provide both immunohistochemical and mutational analysis of the subcutaneous metastases is a case series by Wang et al (18). They describe two patients with abdominal cutaneous metastases and three extra-abdominal cutaneous metastases (two to scalp and one to cheek). All five cases had multiple concurrent or subsequent abdominal and/or hepatic metastases. Immunohistochemical studies for CD117 expression were performed on the cutaneous metastases in all five cases, and all cases were positive for CD117. In addition to this, four out of the five cases were analyzed for KIT mutations in exons 9, 11, 13, and 17. Two of the four cases had mutations in exon 11, and the remaining two cases were wild-type for exons 9, 11, 13, and 17.

Discussion

The development of molecularly targeted therapy against c-KIT and PDGFRA with imatinib and sunitinib has significantly altered the treatment of GIST. Notably, imatinib has been shown to increase progression free survival in advanced disease (19). Most of the somatic mutations in c-KIT are gain-of-function mutations found in exon 11 and exon 9, with exon 11 mutations showing improved objective responses, time to tumor progression, and overall survival in patients treated with imatinib (19). A mutation in exon 11 was present in our patient's malignancy, and she experienced a time to tumor progression of approximately two years while on imatinib. With progression to liver metastases, indicating imatinib resistant GIST, she was started on sunitinib. Despite use of sunitinib, her disease progressed in the form of lung and bone metastases. The clinical activity of sunitinib after imatinib failure has also been correlated with kinase genotype, with progression-free survival and overall survival significantly longer for patients with primary KIT exon 9 mutations or with wild-type genotype, as compared to those with KIT exon 11 mutations (20).

While the relationship between certain kinase genotypes and clinical progression has been described in articles by Heinrich et al (19,20), it remains unclear why some patients develop particularly aggressive and unusual metastases. It is also unclear why expression of CD117 in certain metastatic lesions is diminished or absent, such as in our patient's left

arm subcutaneous nodule. The absence of CD117 may be related to dedifferentiation of the malignancy or associated with changes induced by tyrosine kinase inhibitor therapy. Loss of CD117 expression has been observed in advanced GIST cases, and may itself be a harbinger of imatinib failure and poor prognosis (21,22). We further postulate that the type of mutation, including point, substitution, deletion, or deletion-insertion, may affect clinical aggressiveness and prognosis, as well as response to imatinib and sunitinib, with exon 11 deletions having a more aggressive course. Additional research is needed to elucidate the relationship between the type of mutant genotypes, and the site of metastases, clinical aggressiveness, and response to tyrosine kinase inhibitors.

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