Case Report
A lethal mesenteric gastrointestinal stromal tumor: a case report and review of the literature

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Received July 23, 2015; Accepted August 26, 2015; Epub September 1, 2015; Published September 15, 2015

Abstract: Gastrointestinal stromal tumors (GISTs) arising from the mesentery are very rare. Here, we report a 53-year old man with a huge lobulated cystic-solid tumor in the left lower quadrant of the abdomen, which had been proved clinically and radiographically. Surgical resection showed that the large mass was noted at the mesentery of small intestine. Grossly, the largest diameter of the mass were measured up to 23 cm, and poorly circumscribed. Histological observation demonstrated it as a malignant GIST with positive CD117 (c-kit) staining. Mitotic figures were frequently observed up to 110 per 50 high power fields. Soon after the surgery, the patient experienced local recurrence with quick growth. The patient received targeted therapy (imatinib mesylate) but had no ideal effect. The patient died nine months after the operation because of rapid disease progression.

Keywords: Gastrointestinal stromal tumors, computed topography, immunohistochemistry, CD117, follow-up

Introduction

Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal tumors in the gastrointestinal tract. GISTs outside the digestive tract were called as extra-gastrointestinal stromal tumor (EGISTs) [1]. GISTs are believed to originate from interstitial cells of Cajal or related stem cells [2]. Primary EGISTs are extremely rare, and often arising from the mesentery, omentum or retroperitoneum [3]. As reported in 1999 by Emory TS et al., EGISTs accounts for about 7% of all 1431 cases of GISTs, in which, only 7 cases were found primary originating from mesentery [4]. GISTs are characterized by CD117 (c-kit proto-oncogene product) protein, a tyrosine kinase growth factor receptor, positivity [5].

Primary EGISTs deriving from omentum and mesentery demonstrated clinicopathological and immunohistochemical characteristics similar to a GIST of the digestive tract described previously in the literature [6]. The risk of GIST is measured by its site and size [7]. A high mitotic rate (>5/50 HPF) and a high Ki-67 labeling index (>10%) indicated a significantly poorer outcome of the patients [3]. Completely surgical resection is the only effective treatment approach for GISTs. Recently, imatinib, an inhibitor of tyrosine kinase receptor, has been introduced for the management of advanced and metastatic tumors [8].

Herein, we report a giant highly malignant EGIST at the mesentery of the small intestine of a 53-year old man, with a discussion on its clinical, light microscopic and immunohistochemical features, prognosis and differential diagnosis.

Case presentation

Clinical summary

A 53-year old man was admitted to our hospital with over one-month history of paroxysmal abdominal pain and abdominal distention without other constitutional symptoms. The patient had been taking anti-hypertensive medications for 3 years and denied a history of unhealthful environment and treatment of additional diseases. Physical examination revealed a 14×15 cm hard mass. Laboratory findings were unremarkable and tumor markers, including CEA, CA199, AFP and CA744, were all within the normal limit. A subsequent computed topography (CT) of the abdomen showed a huge lobulated
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cystic-solid tumor in the left lower quadrant of the abdomen, and its size is $17 \times 12$ cm (Figure 1). A curative resection of the mass was performed on a surgical field. The large mass was noted at the mesentery of small intestine, which encroached on the left side of the abdominal wall, proximal jejunum, middle-lower descending colon and upper sigmoid colon.

Pathologic findings

The tumor measured $23 \times 16 \times 12$ cm in size. The tumor was firm or soft and the cut surface showed a grayish yellow to taupe with prominent hemorrhage and necrosis (Figure 2). Microscopically, the tumor was composed of spindle or polygonal cells with eosinophilic cytoplasm, parts of which are arranged like woven or vortex. The tumor cells had large pleomorphic nuclei with conspicuous nucleoli. Mitotic figures were frequently observed up to 110 per 50 high power fields (Figure 3). Immunohistochemical stains of the tumor cells revealed positivity for CD117 (c-Kit) and vimentin. The Ki-67 labeling index for the tumor proliferative activity was 80%. The tumor partly showed positive CD34 and CD68. However, Dog-1, lysozyme, HMB45, S-100 and cytokeratin were totally negative (Figure 4). Molecular genetic analysis (KIT mutation) showed that no mutation was found in exon 12 or 8 of PDGFRA gene and exon 9, 11, 13 or 17 of c-Kit gene (Data are not shown).

Follow-up

At 26 days after surgery, ultrasound test showed a solid hypoechoic mass, $7.5 \times 3.7$ cm in size, considered tumor recurrence in the lower left abdominal. And 9 days later, size of the mass rapidly enlarged to $12.5 \times 10.4$ cm. The patient started imatinib mesylate targeted therapy at 400 mg/day for a half month. Because of ineffective response, drug dosage was increased to 600 mg/day, but still had no effect of therapy. Finally, the patient died about nine months after surgery.

Discussion

Gastrointestinal stromal tumors (GISTs) are c-Kit-positive neoplasms of the digestive tract [9]. GISTs outside the digestive tract called extra-gastrointestinal stromal tumor (EGISTs). Characteristic morphological features and
immunohistochemical positive for CD117 (c-kit) are the main diagnosis basis for GISTs. Moreover, most GISTs express CD34 (70%), and heavy caldesmon (80%), whereas 25% are positive for smooth muscle actin and less than 5% for desmin. It’s important to distinguish mesenteric GIST from mesenteric malignant fibrous histiocytoma (MFH), which usually has the positive immunoreactivity pattern of the tumor cells for vimentin, lysozyme, and CD68. As the immunohistochemical results in the case we report, there is no doubt that this case is a mesenteric GIST. Defining risk of aggressive behavior in GISTs is measured by its site, size and mitotic count [10]. (Table 1) A high mitotic rate (>5/50 HPF) and size (>5 cm) indicate that the tumor is high risk. To the best of our knowledge, EGISTs that arise from the mesentery are very rare with only about 13 previous cases reported in English literature (Table 2) [11-23]. Including this case we present, 9 of 14 were male patients with an average age of 62.4 (the range of 30 to 78) years and 5 were female with an average age of 49.6 (the range of 17-71). All patients were symptomatic, and abdominal distension present in 57% of cases. The tumors were located in the transverse mesentery (n=3), in the jejunal mesentery (n=2), and in the rectal mesentery (n=1), and 7 cases were just reported in the mesentery. The average tumor size was 19.7 (the range of 6 to 35) cm in diameter, and the high mitotic rate (> or =5/50 HPF) present in 66.7% (data of two cases about mitotic rate are missing). All the cases belong to high risk. Mesenteric EGISTs having a higher positive rate of CD117 than those derived from stomach, small intestine, colon and rectum [24]. In these reported cases, the positive rate of CD117 staining is 100%. 13 patients were treated surgically, in which 10 patients were given imatinib after surgery. Out of these four patients present tumor recurrences post-operatively, including two deaths.
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EGISTs were large in size, measuring more than 10 cm [25]. The biggest mesenteric GIST was reported by Nakayama T et al. in 2003, and its size is 35×25×18 cm arising from the mesentery of the rectal mesentry [22]. In this case, the tumor is 23×16×12 cm in size, which is the biggest EGIST arising from mesentery of the small intestine. Its mitotic count is 110/50 HPF, to our best knowledge, which is highest in the previous reports. This tumor was found recurrence so soon after surgery, and imatinib had no effect on the patient. The patient died because of rapid disease progression about nine months after surgery. There is no doubt that this giant mesenteric EGIST is extremely malignant.

Optimal management of GIST requires carefully radiographic, exactly pathologic, systematically medical examination, and completely surgery, even targeted therapy with tyrosine kinase inhibitor, such as imatinib mesylate [26]. Imatinib mesylate [Gleevec], a receptor tyrosine kinase inhibitor, provides an effective treatment for recurrent or metastatic GISTs

Table 1. Proposed modification of consensus classification for selecting patients with GIST for adjuvant therapy

<table>
<thead>
<tr>
<th>Risk category</th>
<th>Tumor size (cm)</th>
<th>Mitotic count (per 50 HPFs)</th>
<th>Primary tumor site</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very low</td>
<td>&lt;2.0</td>
<td>≤5</td>
<td>Any</td>
</tr>
<tr>
<td>Low</td>
<td>2.1-5.0</td>
<td>≤5</td>
<td>Any</td>
</tr>
<tr>
<td>Intermediate</td>
<td>2.1-5.0</td>
<td>&gt;5</td>
<td>Gastric</td>
</tr>
<tr>
<td></td>
<td>&lt;5.0</td>
<td>6-10</td>
<td>Any</td>
</tr>
<tr>
<td></td>
<td>5.1-10.0</td>
<td>≤5</td>
<td>Gastric</td>
</tr>
<tr>
<td></td>
<td>Any</td>
<td>Any</td>
<td>Tumor rupture</td>
</tr>
<tr>
<td></td>
<td>&gt;10.0</td>
<td>Any</td>
<td>Any</td>
</tr>
<tr>
<td>High</td>
<td>Any</td>
<td>Any</td>
<td>Any</td>
</tr>
<tr>
<td></td>
<td>&gt;5.0</td>
<td>Any mitotic rate</td>
<td>Any</td>
</tr>
<tr>
<td></td>
<td>2.1-5.0</td>
<td>&gt;5</td>
<td>Nongastric</td>
</tr>
<tr>
<td></td>
<td>5.1-10.0</td>
<td>≤5</td>
<td>Nongastric</td>
</tr>
</tbody>
</table>

Figure 4. Immunohistochemical staining. The lesion showed diffusely vimentin (A) and CD117 (B) staining. (C) CD34 showed positive staining in the vessels (blue asterisk) and partly tumor cells (red asterisk). (D) The Ki-67 labeling index was used to show the proliferative activity. (×400 original magnification).
### Table 2. Clinicopathological findings of mesenteric EGISTs in the literature

<table>
<thead>
<tr>
<th>Case</th>
<th>Year</th>
<th>Age</th>
<th>Sex</th>
<th>Symptom</th>
<th>Site</th>
<th>Tumor size (cm)</th>
<th>Management</th>
<th>Follow-up</th>
<th>Mitoses/50 HPF</th>
<th>CD117</th>
<th>CD34</th>
<th>CK</th>
<th>Ki-67 (%)</th>
<th>REF.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2014</td>
<td>72</td>
<td>M</td>
<td>increasing abdominal distension</td>
<td>mesentery</td>
<td>23×14×14</td>
<td>surgical resection and imatinib</td>
<td>NA</td>
<td>&lt;5</td>
<td>POS</td>
<td>NA</td>
<td>NEG</td>
<td>NA</td>
<td>[11]</td>
</tr>
<tr>
<td>2</td>
<td>2013</td>
<td>78</td>
<td>M</td>
<td>upper abdominal pain</td>
<td>transverse mesocolon</td>
<td>22×15</td>
<td>surgical resection and imatinib</td>
<td>No evidence of tumor recurrence was identified after 24 months of follow-up</td>
<td>15</td>
<td>POS</td>
<td>NEG</td>
<td>NEG</td>
<td>NA</td>
<td>[12]</td>
</tr>
<tr>
<td>3</td>
<td>2013</td>
<td>69</td>
<td>F</td>
<td>abdominal fullness</td>
<td>mesentery</td>
<td>18×15</td>
<td>imatinib and surgical resection</td>
<td>No recurrence was detected for 16 months after resection</td>
<td>NA</td>
<td>POS</td>
<td>NA</td>
<td>NA</td>
<td>&gt;5</td>
<td>[13]</td>
</tr>
<tr>
<td>4</td>
<td>2012</td>
<td>39</td>
<td>F</td>
<td>low back pain superior to the rectum that radiated down the leg accompanied by nausea</td>
<td>mesentery</td>
<td>8.4×7.7×7.6</td>
<td>surgical resection and imatinib</td>
<td>had a very long time between recurrence of disease</td>
<td>2–3</td>
<td>POS</td>
<td>NEG</td>
<td>NEG</td>
<td>5%</td>
<td>[14]</td>
</tr>
<tr>
<td>5</td>
<td>2010</td>
<td>71</td>
<td>F</td>
<td>increased abdominal circumference</td>
<td>mesentery</td>
<td>20</td>
<td>surgical resection and imatinib</td>
<td>1 1/2 years after the surgery, the patient is asymptomatic</td>
<td>NA</td>
<td>POS</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>[15]</td>
</tr>
<tr>
<td>6</td>
<td>2009</td>
<td>78</td>
<td>M</td>
<td>epigastralgia and abdominal fullness</td>
<td>transverse mesocolon</td>
<td>13×14×15</td>
<td>surgical resection</td>
<td>No recurrence is noted 3 years after the operation</td>
<td>5</td>
<td>POS</td>
<td>POS</td>
<td>NEG</td>
<td>5%</td>
<td>[16]</td>
</tr>
<tr>
<td>7</td>
<td>2007</td>
<td>17</td>
<td>F</td>
<td>menorrhagia</td>
<td>transverse mesentery</td>
<td>30×30×12</td>
<td>surgical resection and imatinib</td>
<td>recurrence</td>
<td>&gt;5</td>
<td>POS</td>
<td>POS</td>
<td>NEG</td>
<td>NA</td>
<td>[17]</td>
</tr>
<tr>
<td>8</td>
<td>2006</td>
<td>42</td>
<td>M</td>
<td>abdominal fullness and pain</td>
<td>mesentery</td>
<td>10×8</td>
<td>imatinib</td>
<td>developed cachexia and died</td>
<td>10</td>
<td>POS</td>
<td>POS</td>
<td>NA</td>
<td>NA</td>
<td>[18]</td>
</tr>
<tr>
<td>9</td>
<td>2006</td>
<td>30</td>
<td>M</td>
<td>severe debilitation, anemia and diarrhea</td>
<td>mesentery</td>
<td>4×6</td>
<td>surgical resection</td>
<td>scarce</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>[19]</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>2006</td>
<td>52</td>
<td>F</td>
<td>abdominal pain</td>
<td>jejunal mesentery</td>
<td>18×14×12</td>
<td>surgical resection</td>
<td>after an 11-month follow-up is doing well</td>
<td>&gt;10</td>
<td>POS</td>
<td>POS</td>
<td>NEG</td>
<td>NA</td>
<td>[20]</td>
</tr>
<tr>
<td>11</td>
<td>2006</td>
<td>63</td>
<td>M</td>
<td>significant for insulin dependent diabetes mellitus and ischemic heart disease, no other clinical symptoms</td>
<td>mesentery</td>
<td>8×5</td>
<td>surgical resection</td>
<td>after 18 month of follow-up showed no signs of recurrent disease</td>
<td>10</td>
<td>POS</td>
<td>NEG</td>
<td>NA</td>
<td>[21]</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>2003</td>
<td>65</td>
<td>M</td>
<td>constipation and abdominal distension</td>
<td>rectal mesentery</td>
<td>35×25×18</td>
<td>surgical resection</td>
<td>died with pneumonia</td>
<td>NA</td>
<td>POS</td>
<td>NEG</td>
<td>NEG</td>
<td>NA</td>
<td>[22]</td>
</tr>
<tr>
<td>13</td>
<td>2002</td>
<td>71</td>
<td>M</td>
<td>satiety</td>
<td>jejunal mesentery</td>
<td>30×24×16</td>
<td>surgical resection and imatinib</td>
<td>8 months after a local recurrence was found; 12 months after the initial surgery showed liver metastases</td>
<td>&gt;10/10 HPF</td>
<td>POS</td>
<td>POS</td>
<td>NEG</td>
<td>NA</td>
<td>[23]</td>
</tr>
<tr>
<td>14</td>
<td>present</td>
<td>63</td>
<td>M</td>
<td>abdominal pain and abdominal distention</td>
<td>mesentery of small intestine</td>
<td>23×16×12</td>
<td>surgical resection and imatinib</td>
<td>26 days after surgery recurrence was found; nine months after surgery the patient died</td>
<td>110</td>
<td>POS</td>
<td>POS</td>
<td>NEG</td>
<td>20%</td>
<td></td>
</tr>
</tbody>
</table>

M = male; F = female; NA = not available; NED = no evidence of disease; POS = Positive; NEG = negative.
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Imatinib resistance is the most important clinical issue in patients with GISTs and its efficiency is closely related to the mutational status of KIT and PDGFRA [28]. However, approximately 10-15% of adult GISTs and 85% of pediatric GISTs lack such mutations, and these “wild-type” GISTs have been reported to express high levels of the insulin-like growth factor 1 receptor (IGF1R), and IGF1R-targeted therapy of wild-type GISTs is being evaluated in clinical trials [29]. Recently, miR-222 and miR-17/20a was reported to directly regulate KIT and ETV1, respectively, which could therapeutically hold great potential for GISTs management, especially in imatinib-resistant patients [30]. Further clinical investigations are urgently needed to characterize the etiology and management of imatinib-resistant in patients of GISTs.

Conclusion

The occurrence of EGISTs is rare and mesenteric EGIST is extremely rare. Its size is usually huge and its risk is almost high. Aggressive surgical intervention is the most effective treatment associated with the use of imatinib. And a strict follow-up is necessary due to high recurrence rates.

Acknowledgements

Written informed consent was obtained from the patient for the publication of this report and any accompanying images.

Disclosure of conflict of interest

None.

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References

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