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Case Report

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

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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

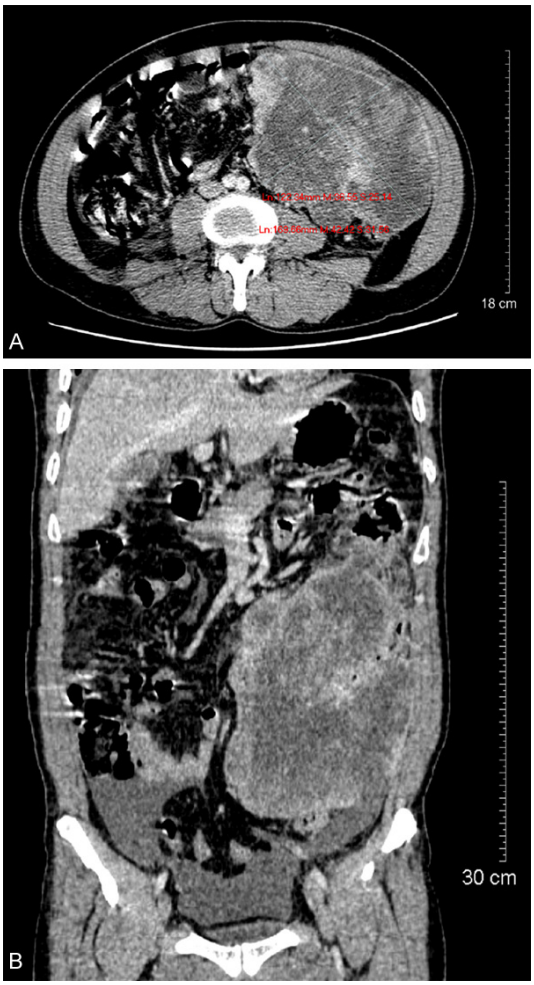

Figure 1. Computed topography (CT) of the abdomen. A. CT scan images showed a huge lobulated cystic-solid tumor in the left lower quadrant of the abdomen. B. The coronal reconstruction image.

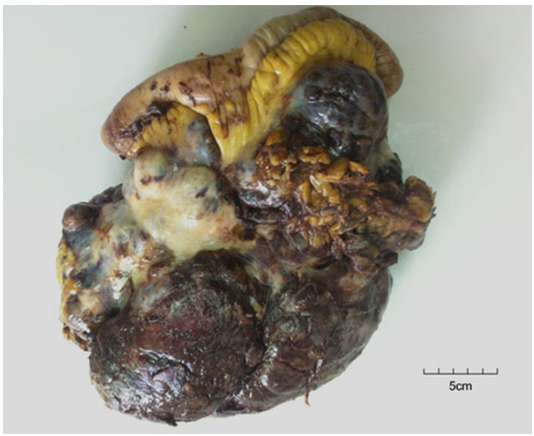

Figure 2. Gross morphology. The tumor was showed a grayish yellow to taupe with prominent hemorrhage and necrosis. The large mass was noted at the mesentery of small intestine.

cystic-solid tumor in the left lower quadrant of the abdomen, and its size is 17×12 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 23×16×12 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, 7.5×3.7 cm in size, considered tumor recurrence in the lower left abdominal. And 9 days later, size of the mass rapidly enlarged to 12.5×10.4 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

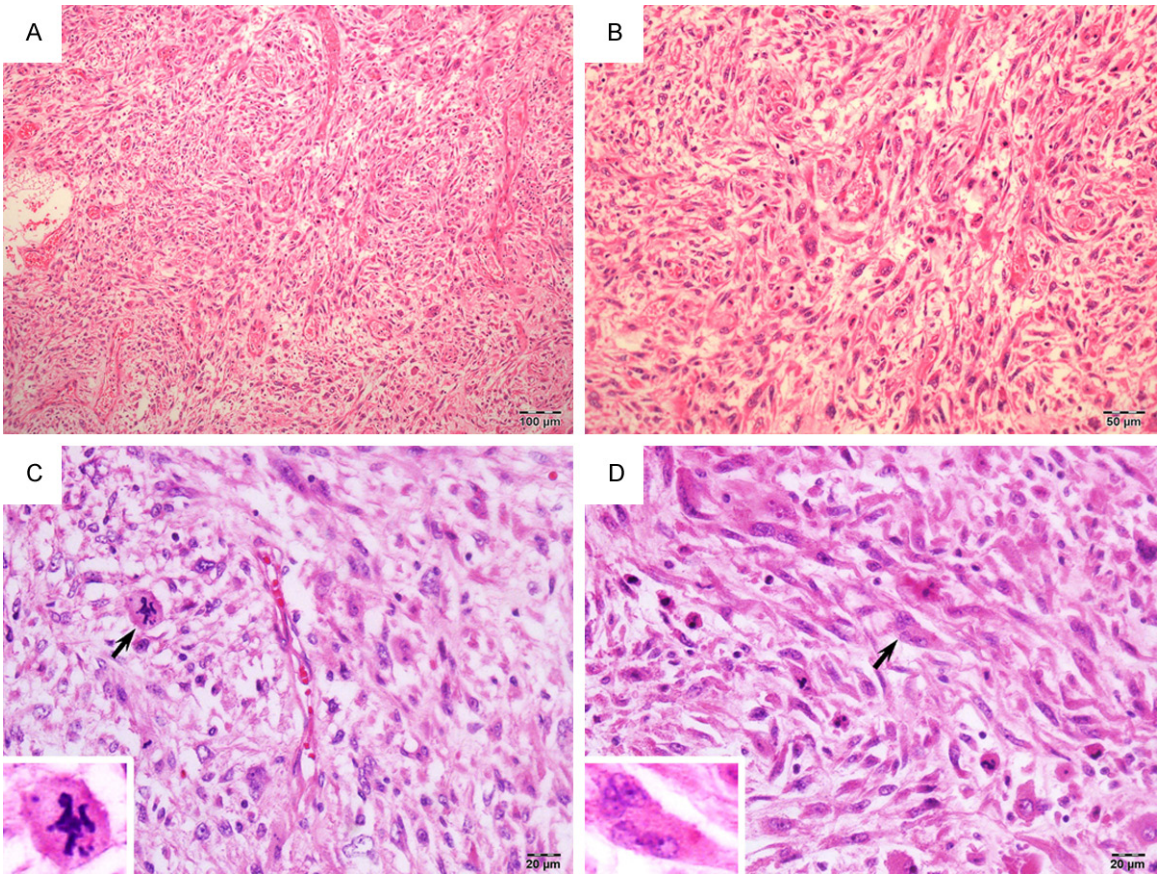

Figure 3. Microscopic features. The tumor was composed of spindle or polygonal cells with eosinophilic cytoplasm, parts of which are arranged like woven or vortex. (A. ×100 original magnification; B. ×200 original magnification). Abnormal mitoses (C) and tumor giant cells (D) were frequently observed (arrow, ×400 original magnification).

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 histocytoma (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.

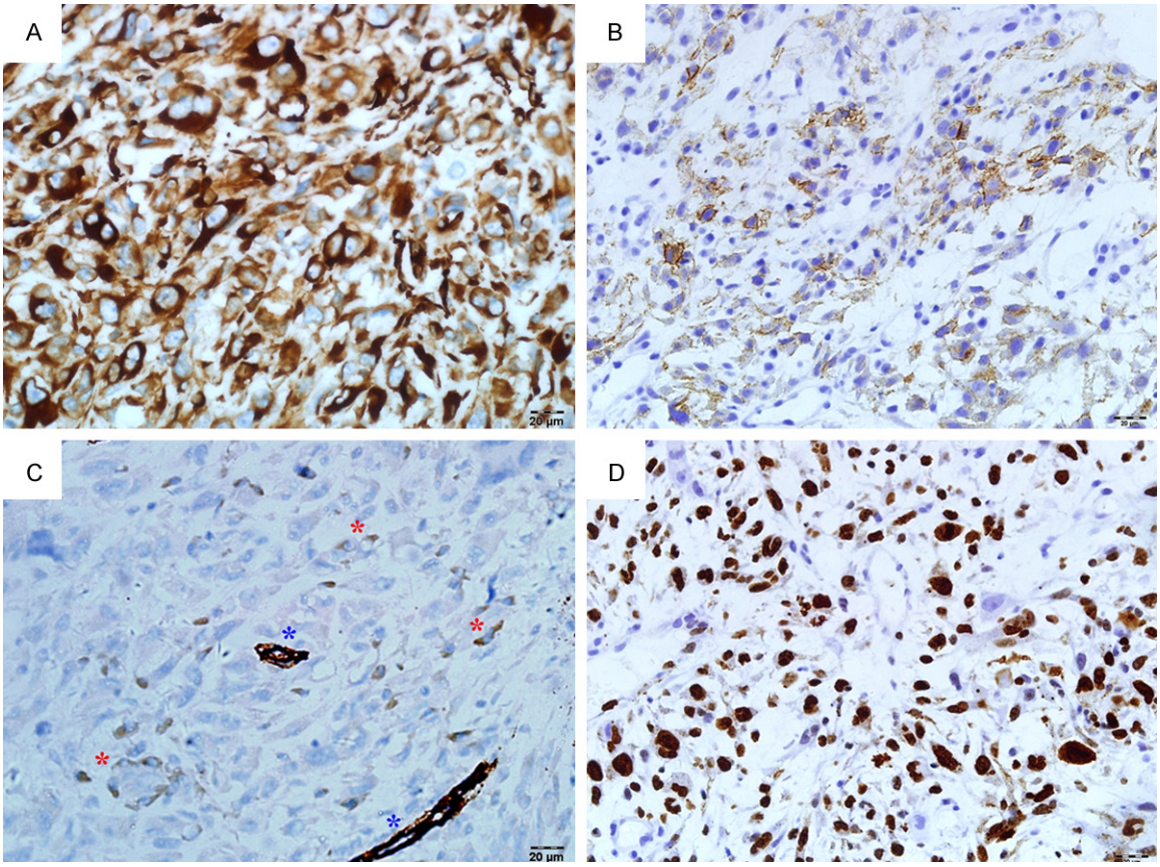

Figure 4. Immunohistochemical staining. The lesion showed diffusely vimentin (A) and CD117 (B) staining. (C) CD34 showed positive staining in the vessels (blue asterisk) and partly tumor cells (red asterisk). (D) The Ki-67 labeling index was used to show the proliferative activity. (×400 original magnification).

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

Risk category	Tumor size (cm)	Mitotic count (per 50 HPFs)	Primary tumor site
Very low	<2.0	≤5	Any
Low	2.1-5.0	≤5	Any
	2.1-5.0	>5	Gastric
Intermediate	<5.0	6-10	Any
	5.1-10.0	≤5.0	Gastric
	Any	Any	Tumor rupture
	>10.0	Any	Any
	Any	>10	Any
High	>5.0	Any mitotic rate	Any
	2.1-5.0	>5	Nongastric
	5.1-10.0	≤5	Nongastric

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 mesentery [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 2. Clinicopathological findings of mesenteric EGISTs in the literature

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

M = male; F = female; NA = not available; NED = no evidence of disease; POS = Positive; NEG = negative.

[27]. 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.

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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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