J Tokyo Wom Med Univ
86(3) 109~115 (2016)

Report

A Case of Gastrointestinal Stromal Tumor of the Small Intestine Presenting as Gastrointestinal Bleeding with Hemorrhagic Shock

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(Accepted March 11, 2016)

A late 40s woman with melena who had been under evaluation for two weeks began to feel dizzy and visited our hospital. She developed hemorrhagic shock due to extensive melena, and was resuscitated in the intensive care unit. Capsule endoscopy performed one week earlier indicated the bleeding point as a submucosal tumor of the small intestine. Abdominal angiography showed tumor staining from the periphery of the jejunal artery. Partial resection of the small intestine including the tumor was performed after laparoscopic cholecystectomy for gallbladder stones, as requested by the patient. Immunohistochemical staining showed positive responses to c-kit, and malignant gastrointestinal stromal tumor (GIST) of the small intestine was diagnosed. Postoperatively, we started treatment with 400 mg/day of_Imatinib Mesilate, which proved effective in preventing recurrence of GIST. As of about 16 months postoperatively, the patient is doing well without any signs of recurrence.

Key Words: gastrointestinal stromal tumor, high risk, Imatinib Mesilate

Introduction

After the concept of gastrointestinal stromal tumors (GISTs) was proposed as a category of gastrointestinal mesenchymal tumors, various reports regarding its diagnostic methods have been published. The development of a GIST is often marked by acute abdominal or gastrointestinal bleeding, and if a GIST of the small intestine presents as gastrointestinal bleeding, emergency treatment is needed. However, the condition is often difficult to diagnose, and definitive diagnosis often remains undetermined before surgery[1]. Here, we report a case of GIST of the small intestine in a patient who experienced dizziness while being examined for severe anemia at another hospital, and who was later examined at our hospital's emergency outpatient department, where she presented with massive melena and fell into shock while in the outpatient infusion room.

Case Report

The patient was a late 40s woman who presented with the chief complaint of melena.

Medical history: cervical cancer (carcinoma in situ) three years ago.

Family history: None in particular.

History of the present illness: In 2012, the patient was examined at a nearby hospital for chief complaints of dizziness, fatigue, and loss of appetite. Advanced anemia with serum hemoglobin (Hb) level of 5.7 g/dL was noted; upper and lower gastrointestinal endoscopy was performed, but the findings showed no abnormality. Abdominal computed

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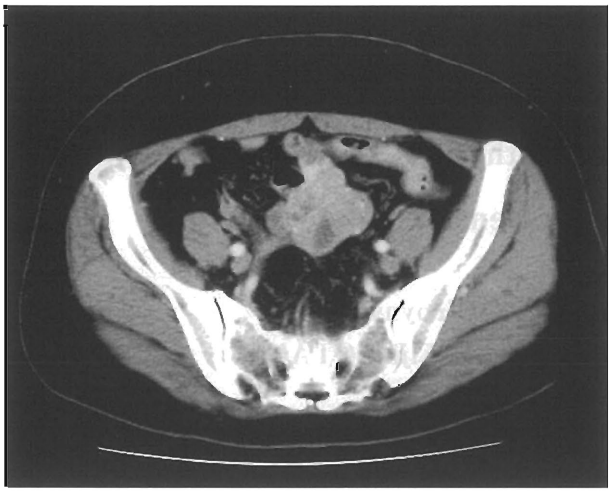

Fig. 1 Contrast-enhanced abdominal CT shows hypervascular tumors of the jejunum located in the lower abdomen

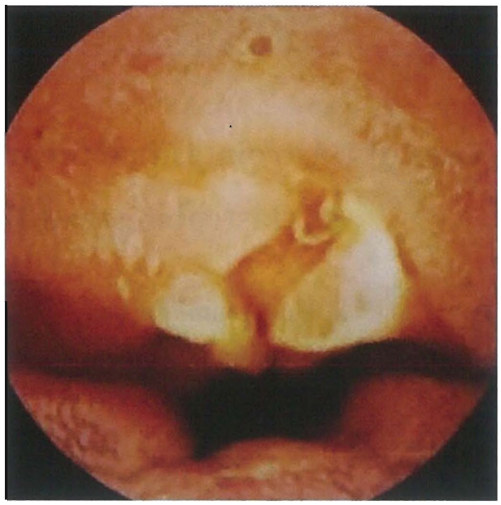

Fig. 2 Capsule endoscopy reveals jejunal ulcer with irregular floor

tomography (CT) revealed a soft mass in the middle of the abdomen; therefore, capsule endoscopy of the small intestine was performed. The test results were scheduled two weeks later, but she was examined at our hospital's emergency room because of her dizzeness. While receiving infusion in the outpatient department, she had massive amount of blood discharge in the stool, her level of consciousness deteriorated to Japan Coma Scale (JCS) III-300, and she fell into hemorrhagic shock. Airway management and fluid resuscitation were performed, and the patient was hospitalized in the intensive care unit (ICU).

The characteristics of the patient and disease at admission were as follows: height 166 cm, body weight 75 kg.

Blood test findings: Blood cell counts: white blood cells (WBC), 5,300/μL; red blood cells (RBCs), 226×10^4/μL; Hb, 6.3 g/dL; and platelets (Plt), 31.6×10^4/μL. Biochemistry: TP, 5.9 g/dL; T-bil, 0.4 mg/dL; GOT, 19 IU/L; GPT, 17 IU/L; LDH, 159 IU/L; BUN, 21.5 mg/dL; Cr, 0.66 mg/dL; Na, 144 mEq/L; K, 3.90 mEq/L; Cl, 110 mEq/L; and CRP, 0.59 mg/dL. Coagulation: prothrombin time (PT), 11.4 s and activated partial thromboplastin time (APTT), 23.9 s.

Abdominal CT findings: A number of calculi were found in the gallbladder. Plain CT on admission failed to indicate the source of bleeding in the gastrointestinal tract; contrast-enhanced CT of the abdomen was performed at a later date, and the findings showed an irregularly shaped tumor mass measuring 6.3 cm in diameter in the middle of the abdomen; the inside of the mass was deeply but unevenly stained (Fig. 1).

Upper gastrointestinal endoscopy: The findings showed only a comb-like reddening in the gastric pyloric antrum.

Lower gastrointestinal endoscopy: Large amounts of black stool were observed, but no apparent source of bleeding could be found.

Capsule endoscopy of the small intestine (performed at the former treating hospital): The test allowed for observation of the entire small intestine, and ulcerative lesions with white fur were found in the upper small intestine (Fig. 2). There was no distinct marginal wall, but the floor of the ulcer was irregular, and the tumor needed to be resected.

Abdominal angiography: Superior mesenteric angiography showed a stained tumor, and feeding blood vessels had developed from the superior mesenteric artery and no active bleeding (Fig. 3).

Bleeding from the hypervascularized tumor of the small intestine was highly suspected based on these findings. Therefore, surgery was scheduled. In accordance with the patient's and her family's wishes, laparoscopic cholecystectomy was performed first, followed by a laparoscopic-assisted resection of the tumor in the small intestine.

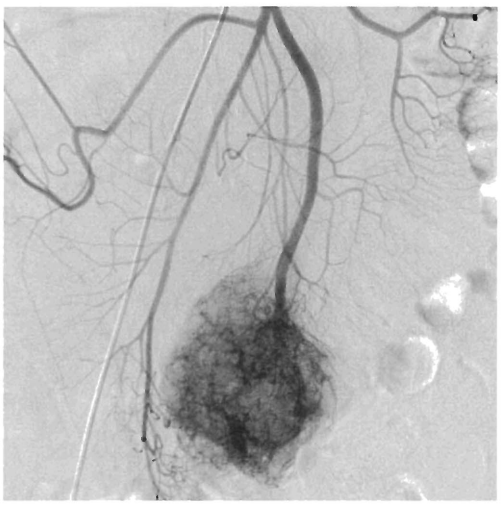

Fig. 3 Superior mesenteric artery angiography reveals the hypervascular mass

Operative findings: The laparoscope was inserted, and the area around the gallbladder was observed; the findings showed that inflammatory adhesions around the gallbladder were mild, and as a result, laparoscopic cholecystectomy was easily achieved. By an extension of the port insertion hole under the navel; and small laparotomy was performed. A tumor protruding in the diverticulum was found on the opposite side of the mesentery of the ileum, and was surrounded by a blood clot and bloody ascites of approximately 100 cc. As found in the preoperative CT scans, the operative findings showed no metastasis to other organs or peritoneal dissemination. Partial resection of the small intestine including the tumor was performed, and the surgery was completed.

Macroscopic findings of the resected specimen revealed a tumor of the small intestine with a diameter of 80 mm, which formed a nodule with a clear margin (Fig. 4).

Histopathological findings: The tumor was composed of spindle cells with a fasciculated growth pattern, and there were more than five mitotic images per 50 HPF. The tumor cells showed no strong atypia, and infiltration by lymphocytes and mastocytes was found between the tumor cells. Immunohistologically, the tumor was positive with the c-kit, whereas the αSMA, CD34, and S-100 proteins were all negative (Fig. 5).

Based on the above, the condition was diagnosed as a high risk GIST of the small intestine.

Oral ingestion of food and liquid was started at postoperative day 3, but the patient developed an intestinal subocclusion at postoperative day 15; therefore, her food intake was limited to a liquid diet. At postoperative day 17, serial fluorography of the small intestine showed good permeability of the anastomosis; therefore, dietary intake including rice porridge was allowed, while the clinical course was kept under observation.

At postoperative day 32, the patient started to receive Imatinib Mesilate (Gleevec®, referred to hereinafter as imatinib), a KIT tyrosine kinase inhibitor, at a dose of 400 mg/day. The patient was discharged at postoperative day 34, and has been treated on an outpatient basis ever since. The doses of imatinib had to be reduced temporarily at one month after initiation because of adverse effects such as muscle pain; however, for approximately 16 months after surgery, the patient is alive and recurrence-free.

Discussion

The incidence of primary malignancies of the small intestine accounts for approximately 1 to 3 % of all gastrointestinal malignancies. According to Yao et al, the incidences of malignancies of the small intestine according to their histological types are as follows, in descending order: cancers, 32.6 %; malignant lymphomas, 30.4 %; and GIST, 29.1 %. GISTs are believed to be the most common among gastrointestinal mesenchymal tumors[2]. In the past, the majority of gastrointestinal mesenchymal tumors were believed to be leiomyomas and leiomyosarcomas, but studies using immunohistochemistry and electron microscopy have revealed that most of them did not actually have the traits of smooth muscles or nerves. Hirota et al found that most GISTs expressed the KIT receptor encoded by the *c-kit* gene; they have also elucidated that the *c-kit* gene contains a high rate of gain-of-function mutations[3]. Immunohistochemically, more than 90 % of GISTs are c-kit-positive, and 60-70 % are CD34-positive. In addition, patients with a gene mutation on the exon 11 of *c-kit* are believed to have a poor

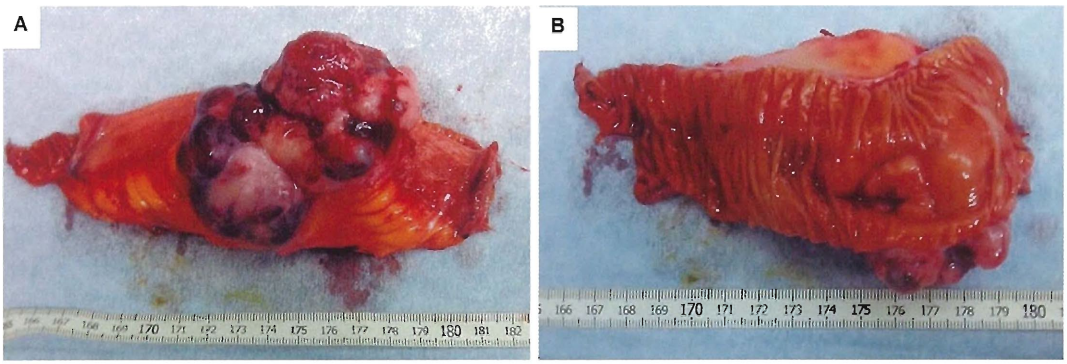

Fig. 4 Resected specimen
A submucosal tumor of the ileum about 80 mm in diameter (A). A hemorrhagic ulceration in the mucosal surface at the tumor (B).

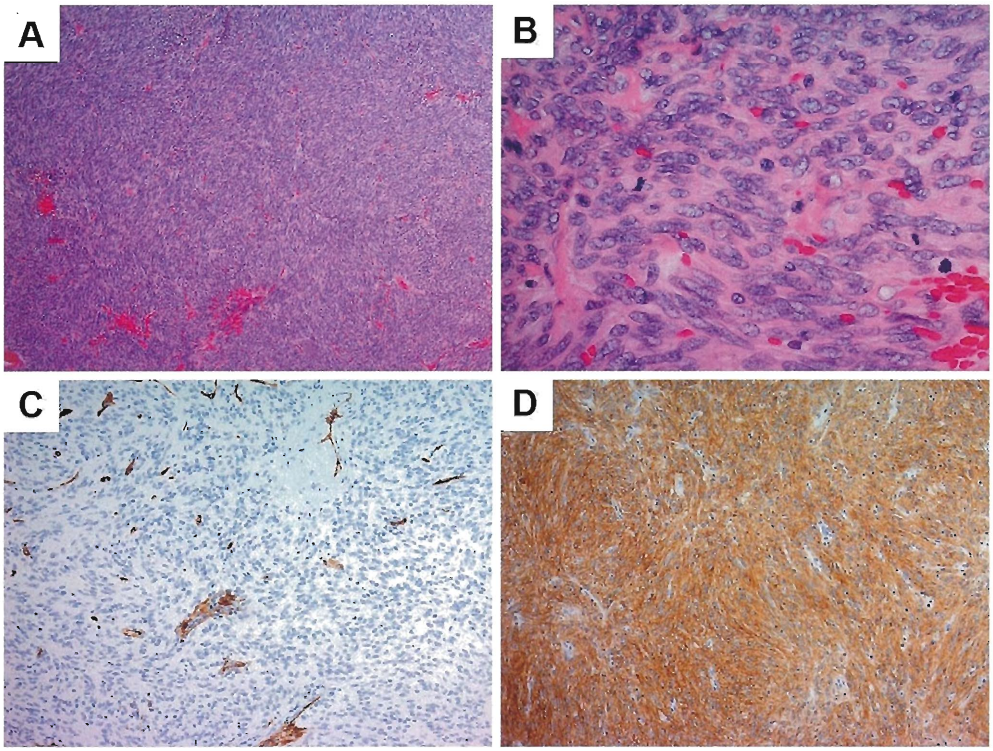

Fig. 5 On histopathology, spindle-shaped cells with mitosis are observed (A, B: Hematoxylin and Eosin stain), negative for CD34 (C), and positive for *c-kit* (D)

prognosis. The platelet-derived growth factor alpha receptor (PDGFRα) has also been reported to contain gain-of-function mutations in some KIT-negative GISTs[4)~6)].

In terms of organs affected by GIST, the small intestine accounts for 15-23 %. On evaluating the degree of malignancy of GIST, the risk of recurrence is classified into four stages on the basis of tumor diameter and mitotic figures (Table 1). However, in terms of the site of GIST, the degree of malignancy is believed to be higher in the small intestine owing to late diagnosis, and the importance of mitotic figures in terms of prognosis is believed to be lower than in the case of GISTs located in the stomach. The case described in this study was that of a GIST in the small intestine. The tumor diameter was 8 cm, and 5 mitotic figures per 50 HPF were found; therefore, the GIST in this study was considered to be of high risk. Other prognostic factors include MIB-1 labeling index and telomerase activity, which

Table 1 Proposed approach for assigning risk to gastro intestinal stromal tumor (GIST)

	SIZE	Mitotic count
Very low risk	<2 cm	<5/50 HPF
Low risk	2-5 cm	<5/50 HPF
Intermediate risk	<5 cm	6-10/50 HPF
	5-10 cm	<5/50 HPF
High risk	>5 cm	>5/50 HPF
	>10 cm	Any mitotic rate
	Any size	>10/50 HPF

HPF: high-power field.

are helpful in predicting the clinical course.

In GIST of the small intestine, the initial symptoms include abdominal pain, palpable abdominal mass, gastrointestinal bleeding, and obstructive symptoms[7)~12)]. There have also been rare reports of perforation due to necrotic changes associated with the enlargement of the tumor[13)]. In the case described in our study, the initial symptoms consisted of dizziness, fatigue, and loss of appetite, and the patient was being examined at a nearby hospital for a detailed checkup. The patient was examined and admitted to our hospital's emergency outpatient department with a chief complaint of dizziness, occurring while she was outdoors; immediately after being examined, she presented with massive melena and fell into hemorrhagic shock while in the outpatient infusion room.

Commonly, useful tests for diagnosing GIST include CT, magnetic resonance imaging, endoscopy of the small intestine, and capsule endoscopy[14)]. In addition, angiography and CT angiography (CTA) are useful because they enable visualization of the tumor and its feeding blood vessels and identifying the location of GIST[15)]. CTA enables detecting GISTs measuring 20 mm or less in the small intestine, which are commonly impossible to visualize with contrast-enhanced CT. The growth patterns of GISTs can be classified into four categories: 1) intramural growth type, 2) intraluminal growth type, 3) extravascular growth type, and 4) mixed type (3). Yanagi et al previously reported that injection of dye from an indwelling microcatheter during angiography was useful for the intraoperative confirmation of the sites of tumors with intraluminal growth in the small intestine, which are difficult to recognize from the surface of the serosal membrane[1)]. However, most cases of GIST of the small intestine tend to be diagnosed late, as in other tumors of the small intestine, and the definitive diagnosis is often based on the resected specimens from emergency surgery performed on patients with acute abdominal or gastrointestinal bleeding.

In the past, radiation therapy and chemotherapy were believed to be virtually ineffective in treating GIST, and surgical resection was believed to be the only radical treatment. Commonly, lymph node metastasis is believed to be rare, and lymphadenectomy is believed to be unnecessary during surgery[16)]. Imatinib was originally developed as a drug that inhibits the tyrosine kinase activity of BCR-ABL protein, which causes chronic myelocytic leukemia; however, because it also inhibits the kinase of PDGFRα and KIT, Imatinib has a potential antineoplastic effect against GIST, and has been approved for insurance coverage in Japan since July 2003.

The recommended period of administration of Imatinib is three years. Adverse effects, including gastrointestinal symptoms such as vomiting and diarrhea, are likely to occur within one week after initiation of administration of treatment; adverse effects such as edema and fluid retention are likely to occur within three weeks, and those including cytopenia, muscle pain and skin symptoms such as a rash are likely to occur after one to two months. The treatments can be administered continuously once the patient gets through those adverse effects. In the case described in this study, the patient received radical surgical treatment, and imatinib therapy was started as a prevention of postoperative recurrence. During the early stages of the administration of imatinib therapy, the doses of imatinib had to be reduced temporarily because of complaints of adverse effects such as muscle pain in the back and lower extremities as well as darkening of the skin; however, these adverse effects started to disappear one month after initiation of treatment, and this has allowed for continuous administration of the specified dosage. Clinical laboratory tests conducted at

six months after surgery showed no recurrence. In patients showing recurrences of GIST, tumor resection may potentially lead to favorable outcomes, even in patients with a long disease-free interval (20 months or longer) between the initial surgery and recurrence. In contrast, even in cases with a low degree of malignancy, recurrences have been reported more than 10 years after surgery[12]. Therefore, long-term follow-up is needed. The case described in this study was in the high-risk group, and in the future, we will conduct a strict long-term follow-up while measuring the blood concentration of imatinib.

Conclusion

We report a case of GIST of the small intestine presenting as gastrointestinal bleeding with hemorrhagic shock. We achieved successful resuscitation and performed definitive surgery with 400 mg/day of Imatinib Mesilate in preventing recurrence of GIST. As of about 16 months postoperatively, the patient is doing well without any signs of recurrence in spite of its malignancy.

The authors declare no conflicts of interest.

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消化管出血による出血性ショックを来たした小腸 gastrointestinal stromal tumor（GIST）の1例

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症例は49歳女性で，2012年末に下血出現し近医で精査中，めまいを自覚し当院を受診した．救急室で大量下血し出血性ショックに陥ったため蘇生処置を，ICUで呼吸循環管理を要した．前医でのカプセル内視鏡と当院での血管造影検査で小腸 gastrointestinal stromal tumor（GIST）と診断し手術を施行した．手術所見は回腸の腸間膜対側に深い潰瘍を伴う内腔に突出した腫瘍を認めた．本人の希望で以前より指摘されていた胆嚢内結石に対し腹腔鏡下胆嚢摘出術を行った後に臍下のポート挿入孔を延長，小開腹で腫瘍を含めた小腸部分切除を施行した．組織標本は最大径80 mmで核分裂像は50 HPFあたり5個以上認めた．また，免疫組織学的には腫瘍はc-kit強陽性でαSMA，CD34，S-100蛋白はいずれも陰性であった．以上よりハイリスクのGISTと診断した．再発予防に術後32日目よりメシル酸イマチニブ400 mg/日を開始した．術後約16ヵ月無再発生存中である．