A 64-year-old man with a chief complaint of melena visited our emergency outpatient clinic. After several examinations, he was diagnosed as a gastrointestinal stromal tumor (GIST) with liver metastasis. Surgical resection of the jejunal lesion and postoperative adjuvant therapy with STI571 for one year was performed. Due to recent immunohistological studies and introduction of STI571, the diagnosis, treatment, and prognosis of GIST are about to change profoundly. Further accumulation of cases is necessary to investigate the diagnosis, treatment, and prognosis of GIST.

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**Key words:** GIST, STI571

**Introduction**

Most gastrointestinal mesenchymal tumors were thought to be myogenic or neurogenic tumors in the past. However, recent advances in immunohistochemistry and molecular genetics have led to the introduction of a classification scheme based on the concept of embryological differentiation. Currently, gastrointestinal mesenchymal tumors are classified into gastrointestinal stromal tumors (GISTs), myogenic tumors, and neurogenic tumors (1). We report a patient who presented with severe anemia due to melena leading to the detection of jejunal GIST with liver metastasis, and review the relevant literature.
jejunal artery (Fig. 3). Upper abdominal dynamic CT revealed an approximately 3×3 cm mass in the hepatic dome, which became high density in the early phase and had a low-density margin and slightly low-dense looking interior in the late phase, suggesting the presence of a liver metastasis (Fig. 4). Based on these findings, a biopsy of the liver tumor was performed, and GIST was diagnosed histopathologically, for which surgery was performed on August 14. As surgical technique, small intestinal resection including the lymph nodes of the mesenterium was conducted and end to end anastomosis was performed. With regard to the lesion in the ileocecum, the mesenterium was separated, and hepatic metastatic lesion was partially resected. Intraoperative endoscopic examination showed that the tumor occupied half of the circumference of the lumen, and had an uneven mucosal surface with areas of hemorrhage, a central depression, and elevated borders (Fig. 5). Grossly, the tumor in the resected specimen was seen as a 5×6 cm mass with a smooth surface, located opposite to the site of attachment of the mesentery 120 cm from the ligament of Treitz and 250 cm from the terminal ileum. The tumor had grown and protruded out from the jejunal wall to invade the adjacent jejunal wall (Fig. 6). In the mesenterium close to the intestinal wall, lymph nodes were enlarged and lying in heaps up to 3 cm in size, and concurrently the uneven irregular lesion which is considered to be peritoneal dissemination was observed in the mesenterium of the ileocecum. Since the tumor had also grown into the lumen, the mode of growth was considered to be the mixed pattern. HE-stained histopathological sections showed proliferation of fusiform tumor cells in a whorl or palisade arrangement, with mitoses of 7/50 HPF. Immunohistologically, the tumor cells were positive for c-kit and CD34, partially positive for α-SMA, and negative for S-100 protein. MIB1 labeling index was approximately 15% (Fig. 7). Postoperative course was uneventful, and chemotherapy using imatinib (400 mg/day) was performed as postoperative adjuvant therapy. Abdominal CT at 1 year after surgery did not reveal recurrence. At that time, imatinib administration to GIST was not covered by health insurance and it was
performed after obtaining approval of the Hospital Ethics Committee as well as the informed consent of the patient based on sufficient explanation.

## Discussion

Before 1970, almost all mesenchymal tumors arising from the gastrointestinal muscularis mucosae were considered to be leiomyomas. In 1962, Stout classified these tumors into leiomyomas, leiomyosarcomas, and leiomyoblastomas (2). However, in 1983, based on electron microscopic and immunohistochemical studies, Mazur and Clark indicated that some of these tumors differentiated into Schwann cells, and a few into smooth muscle cells, and proposed that gastric tumors characterized by spindle cell proliferation be designated gastric stromal tumors (3). Thereafter, gastrointestinal mesenchymal tumors began to be called GISTs. In 1996, Rosai called all nonepithelial tumors arising in the gastrointestinal tract GISTs in a broad sense, and classified GISTs with myogenic markers, neurogenic markers, both markers,
and neither marker into the smooth muscle type, neural type, combined smooth muscle-neural type, and uncommitted type, respectively (4). In 1998, Hirota et al confirmed the expression of c-kit on the surface of gastrointestinal motility-regulating pacemaker cells known as interstitial cells of Cajal (ICCs) and in more than 90% of GISTs, and suggested that GISTs might originate in ICCs, and that mutations in the c-kit gene might be frequently involved in the development of GISTs (5). In this case also, the preoperative diagnosis of jejunal GIST was possible based on the liver biopsy findings that the tumor was immunohistologically positive for c-kit and CD34, partially positive for α-SMA, and negative for S-100. α-SMA and S-100 are markers for leiomyomas and neurogenic tumors, respectively. However, since α-SMA is reportedly positive in 30–40% of GISTs (1), α-SMA positivity can not exclude the diagnosis of GIST. The traditional grading of the malignancy of GIST is based on tumor diameter (5 cm), presence or absence of hemorrhage and necrosis in the lesion, cell density, degree of nuclear atypia, mi-

Figure 6. Macroscopic image of the excised specimen.

Figure 7. Photomicrograph of the resected specimen of the tumor. The tumor displayed spindle appearance (A), c-kit positivity (B), CD 34 positivity (C), and MIB-1 (D). A: HE, B–D: Immunohistochemistry, A–D: ×400.
totic figures (5/50 HPF), and presence or absence of metastasis (4, 6, 7). The GIST reported here was considered malignant based on the following findings: tumor diameter ≥ 5 cm, intratumoral hemorrhage, moderate degree of nuclear atypia with 7/50 HPF of mitotic figures, and liver metastasis, direct invasion into the adjacent jejunal wall. In addition, the MIB-1 (Ki-67) labeling index (LI) was 15%, which assesses the cell proliferation-related antigen Ki-67 by an immunohistological method with monoclonal anti-MIB-1 antibody, and has come into widespread use as an excellent indicator of cell proliferative activity (8). Recently, however, based on the concept that all GISTs have high chances of being malignant, they tend to be classified into high- and low-risk groups according to the predicted risk of recurrence and metastasis instead of histologically classifying them into benign and malignant tumors (1). Thus, the tumor reported here was classified as belonging to the high-risk group. The principle of initial treatment was surgical treatment and it was reported that even if there is metastasis, positive surgical resection including metastatic lesion can provide elongated prognosis (9). With regard to leiomyosarcoma, there are some reports on trans arterial embolisation (TAE) or intra-arterio-arterial chemotherapy for hepatic metastatic lesion (10, 11). With regard to the systemic chemotherapy, Joensuu et al (12) reported in 2001 that imatinib (STI571), which is the molecular targeting therapeutic drug attracting attention in chronic myeloid leukemia, may be effective for c-kit positive GIST. There are several reports describing its efficacy (13, 14). However, at the same time, there are reports describing side effects of STI571, and Demetri et al reported that mild to moderate edema, diarrhea, and malaise occurred in many patients who were administered STI571, and gastrointestinal or intra-abdominal hemorrhage occurred in about 5% of patients (15). To the present patient, STI571 is being administered postoperatively at 400 mg/day and abdominal CT has not revealed its recurrence and as a side effect, only mild diarrhea has been observed. There are reports that positron emission tomography (PET) is useful for the judgment of treatment efficacy and prediction of recurrence after administration of STI571 (16).

Emory et al analyzed 1,004 cases of GIST, and reported that GIST of the small intestine had a poorer prognosis than GIST of the stomach (17). However, GISTs of the small intestine are rarely detected until the onset of symptoms, and many of them have attained a large size by the time of detection. Therefore, the difference in the prognosis of GIST cannot be explained by the difference in location alone. With regard to prognosis of small intestinal GIST diagnosed as pathologically malignant, Crosby et al reported that the 5-year survival rate is about 42% and symptoms included abdominal pain (74%), abdominal mass (72%), gastrointestinal hemorrhage (44%), obstruction bowel (44%), and weight loss (16%), and frequent metastatic site included the liver, peritoneum, and greater omentum (18).

However, the advent of STI571 holds the promise of longer survival. Recently, a possibility is suggested that STI571 has different effects depending on the location of the c-kit gene mutation (19). One report described that GIST lacking mutation in the c-kit gene expressed mutation in PDGF-Rα (20). Therefore, it is considered useful to explore the presence or absence of mutation in the c-kit gene and its location for predicting efficacy of STI571. Joensuu et al have already reported treatment efficacy of imatinib depending on the location of the c-kit gene mutation, supporting its significance (21).

In conclusion, we encountered a patient who presented with melena leading to the detection of jejunal GIST with liver metastasis. Due to recent immunohistological studies and the introduction of STI571, the diagnosis, treatment, and prognosis of GIST are about to change profoundly. Further accumulation of cases is necessary to investigate the diagnosis, treatment, and prognosis of GIST.

References