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Efficacy of Long-Term Adjuvant Therapy With Imatinib Mesylate After Extensive Surgical Treatment for Ruptured Gastrointestinal Stromal Tumors of the Small Intestine With Peritoneal Metastases: A Case Report

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Abstract

Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal neoplasms of the gastrointestinal tract. Although most patients with advanced GISTs benefit from imatinib mesylate (IM) as standard targeted therapy, the optimal duration of adjuvant IM for GIST patients with high risk of recurrence who underwent surgical resection remains unknown. In this article, we present a case of a ruptured GIST of the small intestine accompanied by peritoneal metastases, which was effectively treated by surgical procedure followed by long-term adjuvant therapy with IM. Surgical resection was performed for the ruptured small intestinal GIST, and multitude of peritoneal metastases were cauterized. The patient received adjuvant therapy with IM (400 mg/day) for 12 years without an interruption or a dose change. Peritoneal metastatic recurrence was observed by the follow-up computed tomography scan obtained 12 years after surgery, and surgical resection of the recurrent GIST was performed. The molecular examination indicated a KIT exon 11 deletion mutation in both the primary GIST and recurrent GIST. An additional point mutation was observed in the recurrent GIST in exon 17 that caused resistance to IM. The present case might indicate that extensive removal of the tumor cells through surgery and long-term administration of IM without an interruption or a dose change were important for achieving improved recurrence-free survival in patients with ruptured GISTs of the small intestine with peritoneal metastases.

Keywords

small intestinal GISTs, tumor rupture, peritoneal metastases, imatinib mesylate, secondary resistance

Introduction

Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal neoplasms of the gastrointestinal tract that result from stem cell factor receptor (KIT) or platelet-derived growth factor receptor alpha (PDGFRA) activating mutations.[1] The malignancy potential of these tumors becomes different, with the most important prognostic factors are mitotic rate, tumor size, site in the gastrointestinal tract, and tumor rupture.[2,3] In particular, a ruptured GIST is considered to be associated with a high risk of peritoneal recurrence. Although most patients with advanced GISTs benefit from imatinib mesylate (IM) as standard targeted therapy, secondary resistance to IM with disease progression is observed in approximately half of patients after 2 years of therapy.[4] Furthermore, the optimal duration of adjuvant therapy for patient with a high risk of recurrence is currently unknown.

Case presentation

A 46-year-old Japanese man was admitted to our hospital with dizziness and sudden-onset abdominal pain. His past medical history and family history were unremarkable. On

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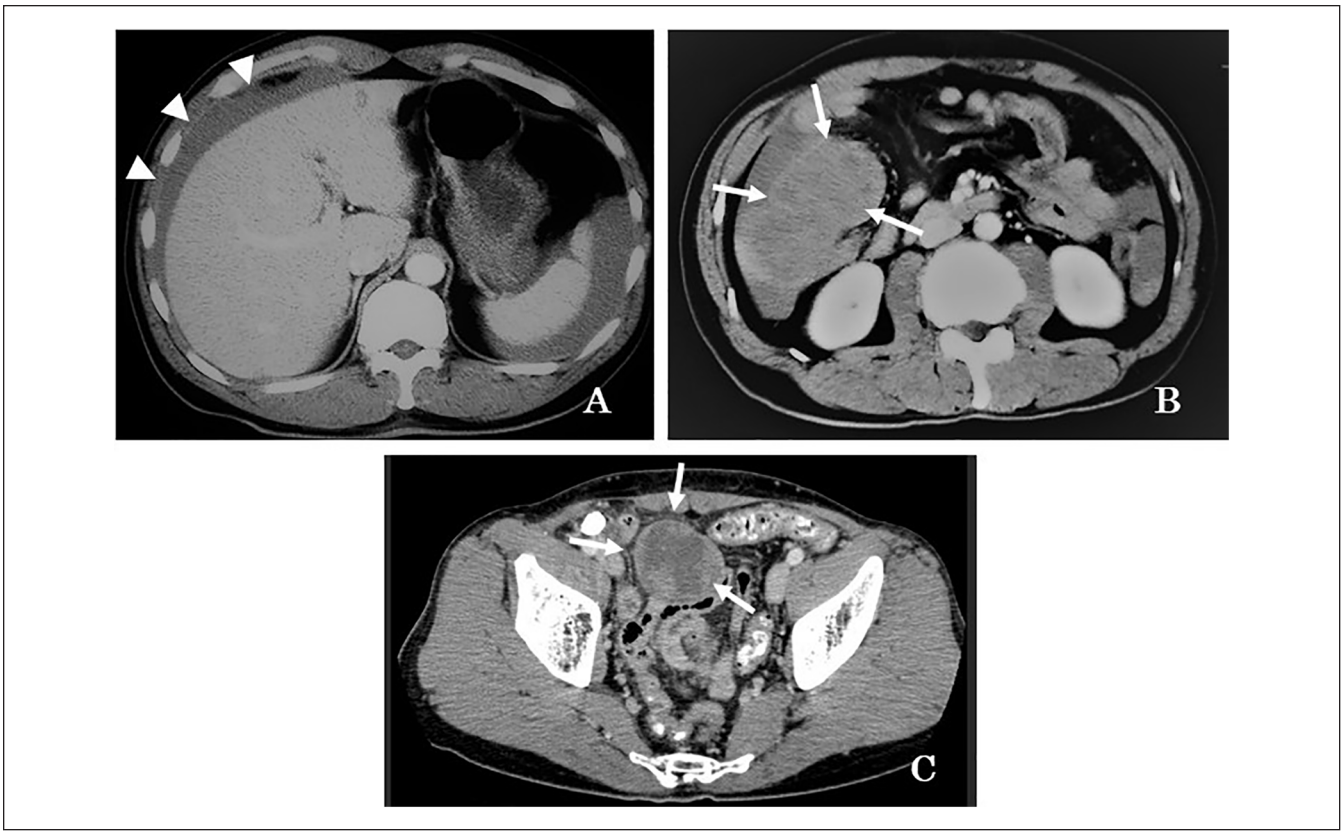

Figure 1. Computed tomography (CT) scan revealed hemoperitoneum (A, arrowheads) and a large heterogeneous mass with a nonuniform enhancement pattern in the pelvis (B, arrows). A follow-up CT scan 12 years after surgery revealed a heterogeneous mass in the abdomen (C, arrows).

physical examination, blood pressure and body temperature were 111/55 mm Hg and 37.3°C. Slight anemia was detected in the palpebral conjunctiva. His abdomen was distended, and tenderness with peritoneal irritation sign on the entire abdomen and a fist-sized palpable mass in lower right abdomen were detected. The laboratory test results were as follows: white blood cell count was 16 500/mm^3, red blood cell count was 372 $\times$ 10^4/μL, hemoglobin was 10.7 g/dL, hematocrit was 32.9%, creatine kinase was 478 IU/L, and C-reactive protein was 0.07 mg/dL. A computed tomography (CT) scan showed fluid collection and a large heterogeneous mass in the abdominal cavity (Figure 1A and B). Based on a diagnosis of intraabdominal hemorrhage from the intraabdominal mass, we performed an emergency operation. Laparotomy revealed a 12 $\times$ 10 $\times$ 6 cm solid tumor in the ileum with bleeding approximately 150 cm from the ligament of Treitz, accompanied by a multitude of peritoneal metastases (Figure 2A). Partial resection of the small intestine including the tumor was performed. Over 80 pieces of peritoneal metastases were individually coagulated by an electric knife. Pathological examination showed that the tumor was composed of spindle cells that were arranged in interlaced bundles with high cellularity (Figure 3A). The number of mitoses was 12 per 50 high-power fields (HPFs; Figure 3A). Immunohistochemical staining showed that the spindle cells were diffusely positive for KIT, CD34, and DOG1 and negative for desmin and S-100 protein (Figure 4). The Ki67 labeling index at the hot spot was 23% (Figure 3B). Based on the above-mentioned findings, the tumor was diagnosed as a high-risk malignant GIST of the small intestine. KIT mutation analysis showed that the tumor had a mutation at exon 11 of the KIT gene. On the 14th postoperative day, an oral administration of IM at 400 mg per day was started. The administration of IM has been performed during 12 years without an interruption or a dose change, because the regimen was well tolerated with no adverse events. The patient has been followed-up for 12 years with no evidence of recurrence. However, 12 years after surgery, follow-up CT revealed a mass 6 cm in diameter in the abdomen (Figure 1C). Positron emission tomography with 18-fluorodeoxyglucose (FDG-PET) revealed no other sites of FDG uptake except for the known tumor in the abdominal cavity. Based on a diagnosis of recurrent GIST, tumor resection was performed. The tumor adhered to the greater omentum but was not invasive (Figure 2B). The few nodules seen on the small mesentery were also resected. The resected tumor measured 7.0 cm in the largest diameter. At the cut surface, the tumor was solid, was gray-white in color, and was

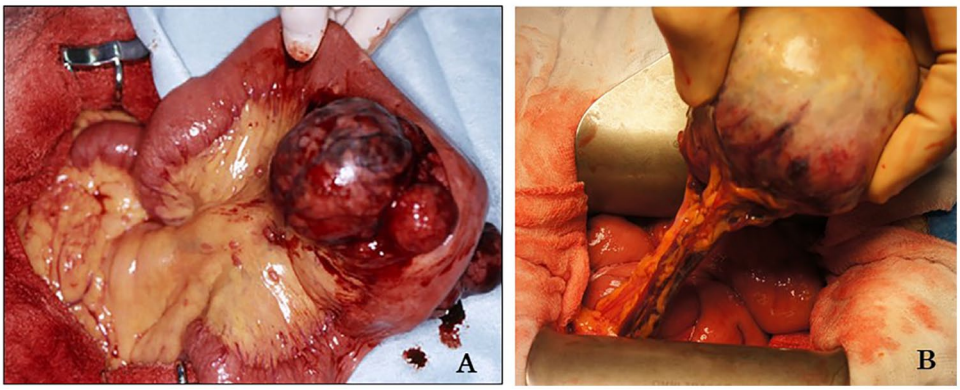

Figure 2. A submucosal tumor of ileum with bleeding was confirmed, accompanied by peritoneal metastases (A). Recurrent tumors adhered to the greater omentum but were not invasive (B).

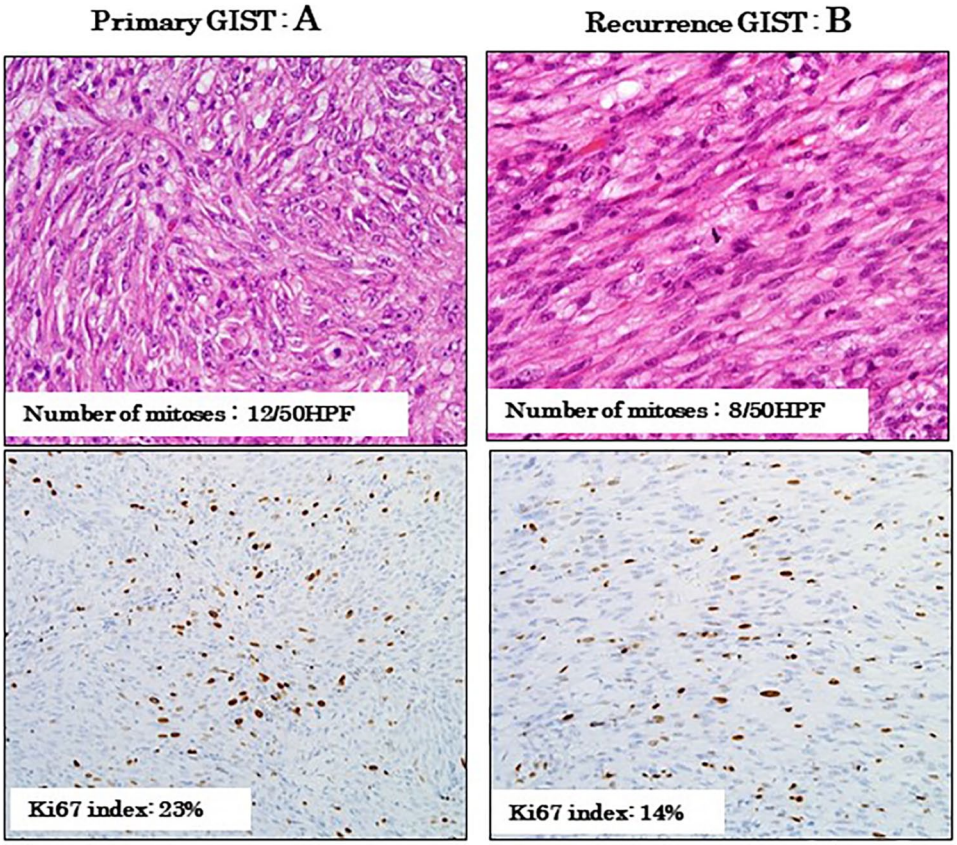

Figure 3. Histology indicated that the primary tumor was composed of spindle cells (A). The number of mitoses in the primary tumor was 12 per 50 high-power fields (HPFs). The histological pictures of the recurrent tumor were almost identical to those of the primary tumor, and the number of mitoses in the recurrent tumor was 8 per 50 HPF (B). Ki67 labeling index was 23% and 14% for the primary tumor and the recurrent tumor, respectively.

associated with extensive hemorrhagic and degenerative changes. Histologically, the tumor was composed of spindle cells proliferating with high cellularity, and hemorrhagic and necrotic tendencies were observed. The number of mitoses was 8 per 50 HPF (Figure 3B). Immunohistochemical analysis showed that the spindle cells were positive for KIT, CD34, and DOG1 and negative for desmin and S-100 protein (images not shown). Ki67 labeling index at the hot spot was

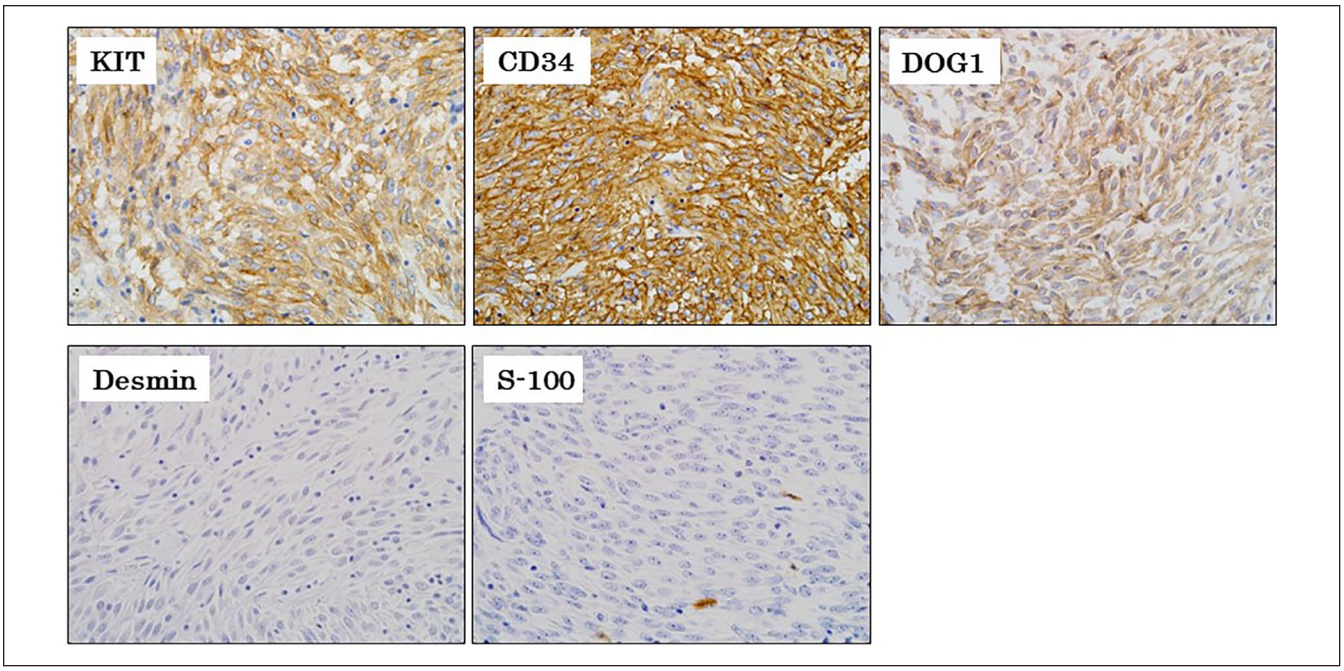

Figure 4. Immunohistochemical staining of primary tumor showing positive reactivity for KIT, CD34, and DOG1. There was no expression of desmin or S-100 protein.

14% (Figure 3B). The histological pictures were almost identical to those of the specimen resected during the first surgery, confirming the diagnosis of recurrent GIST. The molecular examination indicated KIT exon 11 deletion mutations from Trp-557 and Lys-558 in both the primary GIST and recurrent GIST. Additionally, a point mutation was observed in the recurrent GIST in exon 17 from Asp-822 to Lis-822. The patient is currently being administered sunitinib instead of IM and has remained alive without any other recurrences 14 years after the first surgery.

Discussion

Gastrointestinal stromal tumors are the most common mesenchymal neoplasms of the gastrointestinal tract.[1,5] The most common clinical presentation of GISTs is gastrointestinal bleeding. Additionally, acute abdomen due to tumor rupture, obstruction, abdominal pain, early satiety, bloating, or fatigue related to anemia can occur. Approximately 96% of GISTs are positive for KIT by immunohistochemistry. CD34 can be expressed by 60% to 70% of the tumors, and SMA expression is detected in 30% to 40% of the cases.[6] S-100 protein, keratins, and desmin are rarely expressed in GISTs (up to 5%).[6] In molecular biology evaluations of GISTs, the activating mutations in PDGFRA or KIT are observed, which are the key molecular drivers in tumor pathogenesis. KIT mutation are frequently observed in exon 11 (70%) or exon 9 (10%), whereas exons 13 or 17 are rarely involved.[7] Approximately 3% of all GISTs have PDGFRA mutations instead of KIT mutations.[8] Some studies have shown that KIT exon 11 mutations were associated with better response to IM and better outcomes than KIT exon 9 mutations and tumors without a detectable KIT mutation.[9]

The malignancy potential of GISTs becomes different, with the most important prognostic factors are mitotic rate, tumor size, site in the gastrointestinal tract (stomach or others), and presence of tumor rupture.[2,10,11] The mitotic count significantly relates to the prognosis of the cases and is expressed as the number of mitoses for a total area of 5 mm^2, in which the value evaluated for the conventional 50 HPF should be converted.

Small intestinal GISTs tend to have an even worse outcome than GISTs of the stomach. Extramural growth tumors correlated significantly with small intestinal location and frequency of peritoneal dissemination probably as a consequence of tumor rupture or due to microscopic serosal penetration.[12] Nishida et al revealed that the incidence of rupture in GISTs was approximately 3%, and both median recurrence-free survival (RFS) and overall survival were shorter with ruptured GISTs than nonruptured GISTs because of their high recurrence rate due to peritoneal metastases.[13]

Although Ki67 expression is not the parameter of high-risk GIST, a Ki67 labeling index >5% was strongly correlated with a worse prognosis.[14,15] High-risk GIST patients with Ki67 labeling index >8% should be clinically followed-up because of the higher possibility of recurrence, even with IM-based adjuvant therapy.[16] Thus, the present patient was expected to have a high risk of recurrence and poor prognosis, because the tumor was large, located in small intestine, ruptured with peritoneal metastases, and had high level of mitotic count and Ki67 labeling index.

After surgical removal of the primary GIST, tumor recurrence is frequent, the median time to progression is approximately 2 years,[4] and approximately 50% of patients died within 5 years of the initial diagnosis.[17] In terms of follow-up for GISTs, there is no standard postoperative follow-up protocol for patients who undergo surgical resection of a primary GIST. CT scan of the abdomen and pelvis with contrast medium is preferred method for follow-up of GIST patients because metastases outside of the abdomen or pelvis are extremely rare.[7,18] It is recommended that high-risk GIST patients treated with adjuvant therapy could be followed-up with CT every 6 months for 3 years during adjuvant therapy, at 3 to 4 months intervals during the first 2 years after stopping adjuvant therapy, and then once every 6- to 12-month intervals until the end of 10 years of follow-up.[19]

When progression is suspected, other imaging may be considered such as magnetic resonance imaging or FDG-PET, which can be helpful in cases with confusing diagnostic images evaluated by CT or for the early prediction of tumor response.[20] In the present case, we performed abdominal and pelvic CT with contrast medium as follow-up imaging once every 6 months during the first 3 years after surgery, after which imaging was performed once a year. After the second surgery, we performed follow-up imaging once every 6 months.

Although most patients with advanced GISTs benefit from IM as standard targeted therapy and treatment with IM for at least 3 years is recommended to improve their RFS and overall survival,[21] secondary resistance to IM with disease progression is observed in approximately half of the patients after 2 years of therapy.[4] On the other hand, it is reported that over 50% of patients with metastatic and/or unresectable GISTs respond to the treatment with IM with the median RFS of more than 2 years, and some patients showing a stable response continuing more than 10 years as observed in the present case.[4,22,23] Currently, it is thought that secondary resistance is largely due to the polyclonal emergence of resistant subpopulations harboring different KIT secondary mutations that are not random but cluster in 2 regions of the KIT kinase domain: the ATP binding pocket (encoded by exons 13 and 14) and the activation loop (encoded by exons 17 and 18).[24] The presence of a KIT exon 11 deletion or indel mutation, which involved codons 557 and/or 558, similar to that found in the present case, was significantly associated with an unfavorable RFS in patients who received 1 year of IM treatment, but no such associations were present among patients who received 3 years of IM treatment.[25]

Sunitinib malate is recommended for the treatment of GIST after disease progression under IM treatment or intolerance of IM because of adverse events.[26] Dosage escalation of IM up to 800 mg daily is another option for disease progression, and it may prolong the median time to progression by 3 months.[27] In the present case, the patient is currently receiving sunitinib malate instead of IM and remains alive without any other recurrences for 14 years after the first surgery.

Although the extensive coagulation of a multitude of peritoneal metastasis was not standard procedure for the malignancy accompanied by peritoneal dissemination, we adapted this procedure for the purpose of removal of as much tumor tissue as possible. From the point of view of cytoreductive surgery, the possibility of the contribution for achieving improved RFS remains the extensive coagulation of a multitude of peritoneal metastases, in addition to chronic treatment of IM.

Conclusion

Herein, we presented a case of a ruptured GIST of the small intestine treated with IM, and observed peritoneal metastatic recurrence due to secondary resistance 12 years after surgery. Although the value of combining surgery and IM therapy for patients with metastatic GISTs is unclear, the present case might indicate that extensive removal of the tumor tissue through surgery and long-term administration of IM without an interruption or a dose change are important for achieving improved RFS in patients with ruptured GISTs of the small intestine with peritoneal metastases, even if removal of the peritoneal metastases is usually followed by subsequent recurrence.

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Declaration of Conflicting Interests

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Ethics Approval

Our institution does not require ethics approval for reporting individual cases.

Informed Consent

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

List of abbreviations

Asp; aspartic acid, CT; computed tomography, DOG1; discovered on GIST-1, FDG-PET; positron emission tomography with 18-Fluorodeoxyglucose, GIST; gastrointestinal stromal tumors, HPF; high power fields, IM; imatinib mesylate, Lis; lysine, Lys; lysine, OS; overall survival, PDGFRA; platelet-derived growth factor receptor alpha, RFS; recurrence-free survival, Trp; triptophan.

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