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Case Report

Neoadjuvant Chemotherapy for Duodenal GIST: A Case Report

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The principal treatment for gastrointestinal stromal tumors (GISTs) is surgical; and complete excision is important, but cannot always be achieved. For such cases, neoadjuvant chemotherapy (NAC) with imatinib mesylate (IM) has been recommended. A case of a GIST of the second portion of the duodenum for which pancreatoduodenectomy was indicated, and for which partial resection was made possible as a result of cytoreduction by IM NAC, is reported. A 64-year-old man with pancytopenia due to hepatic cirrhosis caused by hepatitis C infection received repeated blood transfusions because of anemia of unknown origin starting 2 years earlier. Most recently, the patient had melena with hemoglobin of 5.1 mg/dL. Diagnostic imaging showed a solid tumor, 55 $\times$ 48 $\times$ 65 mm^3, in the second portion of the duodenum showing mainly extramural development. Endoscopic aspiration biopsy showed proliferation of KIT-positive spindle-shaped heterotypic cells. GIST was diagnosed, and an exon 11 KIT mutation was found. Because of the exon 11 mutation, neoadjuvant IM was started at 400 mg/day and then eventually maintained at 300 mg/day for 10 months. Regular CT examinations showed gradual tumor shrinkage. At surgery, a tumor with strong extramural growth was found on the outer side of the duodenum that invaded the retroperitoneum. The tumor was excised as a mass, and the duodenum was resected partially. There has been no recurrence at 9 years postoperatively. Evaluating KIT exon mutations and predicting the effectiveness of NAC appear useful for determining the treatment policy for advanced GISTs.

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The principal treatment for gastrointestinal stromal tumors (GISTs) is surgical, and excision without leaving any remnants is important. However, there are many cases when extensive excision at the time of discovery is difficult or extended surgery is necessary. For such cases, neoadjuvant chemotherapy (NAC) with imatinib mesylate (IM) has recently been recommended as an option for decreasing the extent of resection and surgical morbidity by downsizing the tumor. The cytoreductive effect of IM depends on its dosage, duration, and KIT exon mutations [partial response (PR) and complete response (CR): 7%–66%].[1,2] The dosing period, dosage, and so on used in NAC have varied, and there is no standard treatment at present. For borderline resectable GIST, the downsizing effect is important, and it is said to be necessary to confirm the therapeutic effect in the early period after starting treatment.[3]

Although the frequency of GIST in the duodenum is small, 50% develop bleeding, and pancreaticoduodenectomy (PD) is required in 20%–40% of cases based on the site and size. Compared to limited duodenal resection (LR), PD involves marked surgical invasion with significant morbidity and possible mortality, and postoperative quality of life is poor.[4,5] Although the prognosis is affected by the characteristics of the tumor, it is said that there is no difference based on the operative procedure, and minimizing the extent of surgery is recommended. A case of a GIST of the second portion of the duodenum for which PD was indicated, and for which partial resection was made possible as a result of cytoreduction by means of long-term preoperative IM administration, is reported. Comorbidities included repeated gastrointestinal bleeding and cirrhosis accompanied by pancytopenia and diabetes. Fine-needle aspiration biopsy was performed endoscopically, and GIST and KIT exon 11 mutations were diagnosed before treatment. Preoperative administration of IM was selected with the expectation of high efficacy.

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The patient was a 64-year-old man with pancytopenia due to hepatic cirrhosis caused by hepatitis C infection. Two years earlier, he received a blood transfusion because of anemia (hemoglobin 7.4 mg/dL), but the cause was unclear. Two subsequent transfusions were performed due to exacerbation of the anemia. Most recently, the patient had melena; hemoglobin levels decreased to 5.1 mg/dL and he was hospitalized by his previous physician.

After hospitalization, upper gastrointestinal endoscopy showed submucosal tumors with a beaded appearance on the contralateral side of the ampulla of Vater on the proximal side of the second portion of the duodenum, with ulcer formation (Fig. 1a). Endoscopic biopsy was not diagnostic. Hypotonic duodenography also showed a shadow defect over half of the duodenal opening (Fig. 1b). Computed tomography (CT) and magnetic resonance imaging (MRI) showed hypertrophy of the left lobe of the liver, atrophy of the right lobe, splenomegaly, and a solid tumor of 55 × 48 × 65 mm in the second portion of the duodenum that had progressed mainly extramurally (Fig. 1c, 2a). Angiography for transcatheter arterial embolization showed that the lesion received abundant blood flow from the right hepatic artery, middle colic artery, and gastroduodenal artery, but the bleeding point was unclear (Fig. 1d). The patient was transferred to our hospital for surgery. Positron emission tomography (PET) showed mild accumulation (SUVmax: 3.22) in the tumor, but there was no accumulation elsewhere. Endoscopic aspiration biopsy using a commercial device (21G Endosonopsy, Hakko Shoji, Tokyo, Japan) showed proliferation of spindle-shaped heterotypic cells that were KIT-positive. A diagnosis of GIST was made. KIT mutation status was tested, and an exon 11 mutation was found. The blood data showed hepatitis C virus antibody-positive, hemoglobin of 8.9 mg/dL, WBCs of 3290/μL, platelets of 15.6×10^4/μL, albumin of 3.0 g/dL, AST/ALT of 38/47 IU/L, and an indocyanine green (ICG) 15-minute value of 9%. These data were judged to represent child A cirrhosis of the liver.

Although PD is required for complete resection, it was judged to be excessively invasive given the liver function. The presence of pancytopenia was considered to make sufficient administration of IM difficult. However, because there was an exon 11 mutation, and a cytoreductive effect could be expected, neoadjuvant IM was started at 400 mg/day, having obtained fully informed consent. After 2 weeks, neutrophils were 1100/mm^3, platelets were 9.8×10^4/μL, and AST/ALT was 79/109 IU/L. After

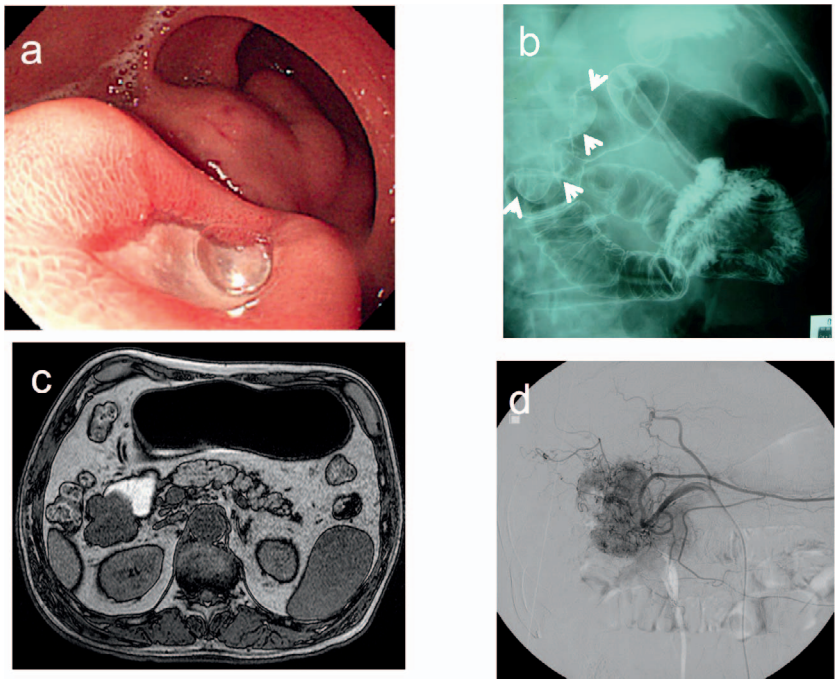

Fig. 1 (a) Upper gastrointestinal examination shows large submucosal tumors in the second portion of the duodenum with ulceration. (b) Hypotonic duodenography shows a defect of the lateral side (white arrows) of the second portion of the duodenum. (c) MRI shows a large solid tumor in the second portion of the duodenum. (d) Angiography shows a hypervascular tumor.

a pausing treatment for 1 week, IM was restarted at 300 mg/day. Laboratory results were checked every 2 to 4 weeks, and neutrophils were found to be in the range of 1090–1480/mm^3, AST/ALT in the range of 60–100 IU, and platelets in the range of 7.0–9.8 $\times$ 10^4/μL. Therefore, the dose was continued at 300 mg/day.

CT was performed every 3 months and showed that the tumor shrank gradually, while side effects were mild and no gastrointestinal bleeding was observed. IM was continued. Platelets decreased to 8.1 $\times$ 10^4/μL, and 15-minute ICG also decreased to 25%. As a result, IM administration was discontinued after a total of 10 months. Images also showed that the tumor shrunk to 30 $\times$ 28 $\times$ 40 mm (Fig. 2b), and surgery was performed 11 months after the start of treatment.

At surgery, the liver showed right lobe atrophy and left lobe enlargement, and its surface was granular. A tumor with strong extramural growth was found on the outer side of the lower duodenum, and it invaded the retroperitoneum. The tumor was excised as a mass from the retroperitoneum, and the duodenum was also resected while confirming the tumor margin. The duodenum was partially cut out in an elliptical shape on the opposite side of the head of the pancreas. The resection was closed with Albert-Lembert suture perpendicular to the intestinal tract.

In the excised specimen, extramural growth was large, the mucosal surface showed a two-humped protuberance, and the scope of duodenal dissection was 50 $\times$ 35 mm (Fig. 3a and 3b). Histologic examination showed a GIST with a typical spindle cell pattern of tumor cells. Immunohistochemically,

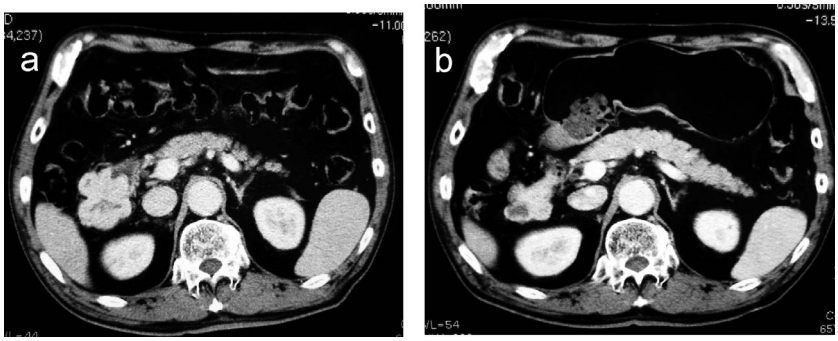

Fig. 2 CT scans show shrinkage of the hypervascular tumor in the second portion of the duodenum. (a) Before NAC. (b) After NAC.

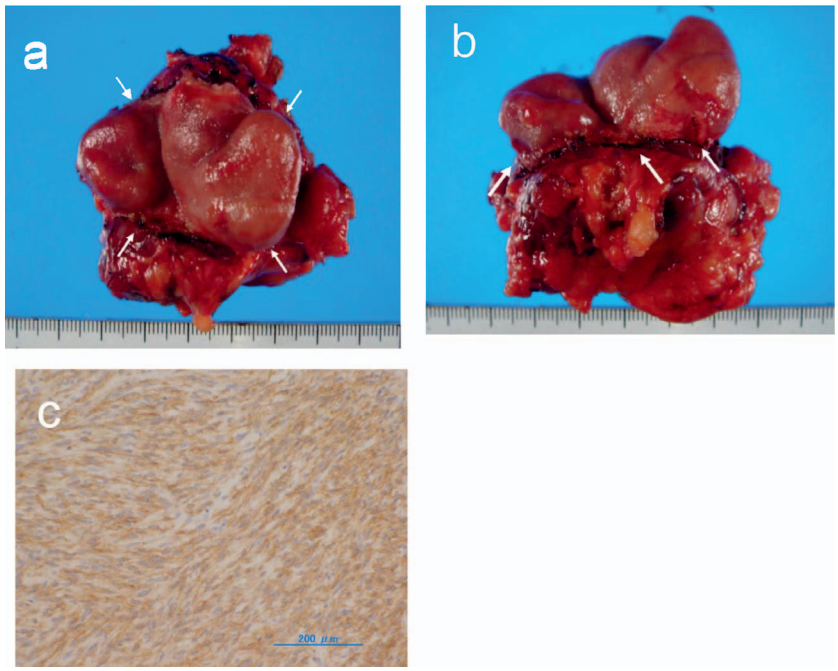

Fig. 3 (a) Macroscopic appearance of the resected specimen (arrows: duodenal wall edges). (b) Lateral view of the specimen showing the tumor extending into the retroperitoneum (arrows: duodenal wall). (c) Immunohistochemically, the spindle tumor cells show c-KIT expression (×50).

the tumor cells were found to be positive for c-KIT and vimentin, but negative for s-100, αSMA, desmin, and CD34 (Fig. 3c). Images of mitosis were seen in 6 to 10/50 high power fields, and MIB-1 was 1%. The modified Fletcher classification was high risk.[6] The patient's postoperative course was good, and the patient was discharged on the 14th day. Although the patient refused postoperative IM administration, there has been no recurrence at 9 years after the surgery.

Discussion

GISTs are rare tumors and the most common mesenchymal tumors of the digestive tract.[6–8] Duodenal GISTs are considered extremely rare, comprising only 3% to 5% of gastrointestinal primary tumors.[8] Duodenal GISTs are often found by chance, and there are few symptoms. However, although it depends on their size (mean 4.5 cm: 1–25 cm), they can show a frequency of gastrointestinal bleeding that is higher than at other sites.[4,9] In general, duodenal GISTs most frequently involve the second portion of the duodenum, followed by the third, fourth, and first portion.[4,5]

The treatment of choice for primary GIST is surgical resection, provided that it is resectable.[3] Surgical resection with microscopically clear resection margins seems to be the only curative treatment.[10] Lymph node metastasis is rare, and lymph node dissection is not necessary.[11] Although partial resection aimed at preserving the internal organs and organ functions is recommended, extended resection may be necessary depending on the size and location of the tumor. Treatment of GISTs in the duodenum is based on the same principle, but the mesenteric side becomes the head of the pancreas, and the operative procedure varies depending on the location and size of the lesion. PD is performed for about 20% to 40% of cases, and LR for 60% to 80%. The prognosis differs according to the biologic characteristics, but it is said to be unaffected by the surgical procedure. Furthermore, since PD is highly invasive and has many complications, LR should be considered first.[4,5]

IM is a competitive inhibitor of KIT. IM shows high therapeutic efficacy for advanced or metastatic GISTs and is reported to be useful for postoperative adjuvant therapy.[12] Recently, preoperative administration of IM is beginning to be performed, so that less invasive surgery is possible due to tumor shrinkage. In a phase 2 study, the European Organization for Research and Treatment of Cancer, Soft Tissue, and Bone Sarcoma Group Experience,[13] IM was administered to 161 patients with GISTs for 10 months; 80% of the cases showed tumor shrinkage, and organ preservation exceeded what had been planned. In a multi-institutional prospective trial (Radiation Therapy Oncology Group),[1] 63 patients were administered IM at 600 mg for 2 to 3

months, and postoperative complications and drug toxicities were reported to have been few. For the 31 cases of primary GIST among them, the response evaluation criteria in solid tumors (RECIST) was PR in 7% and stable disease (SD) in 83%. However, in both studies, the number of cases was small, there was combined use of postoperative adjuvant therapy and other treatments; and at this time, the results are insufficient as the basis for proactively recommending NAC. Ramaswamy *et al*[2] conducted NAC for 5 months (median) for 76 cases of GIST, and RECIST was stated as CR in 1%, PR in 64%, SD in 23%, and PD in 5.2%, suggesting the effectiveness of long-term administration. Even in the European Society for Medical Oncology guidelines,[3] the indication for IM pretreatment is limited to when the lesion cannot be completely resected, when total gastrectomy becomes overly invasive, and so on, but there are no specifics regarding its administration. It is important to confirm the therapeutic effect in the early period after starting treatment, or to confirm the therapeutic efficacy by performing mutational analysis.

Analysis of KIT mutation status is considered to be useful for predicting the therapeutic effect of IM. In the B2222 study (a phase 2 study of IM),[14] c-KIT mutation analysis was performed for 127 GIST patients, and the reported response rates were 83.5% for exon 11 mutation cases, 47.8% for exon 9 mutation cases, and 0% for the wild type. The Cancer and Leukemia Group B 150105 study[15] investigated 428 patients with GIST, and the response rates with IM were reported to be 71.7% for exon 11 mutation cases, 44.4% for exon 9 mutation cases, and 44.6% for the wild type. When the response to IM is insufficient, a change to sunitinib malate is considered. It has shown remarkable efficacy in some cases,[16] and a greater effect can be expected in patients with an exon 9 mutation. Sunitinib malate is another small-molecule tyrosine kinase inhibitor currently licensed for use in imatinib-refractory GIST. In a phase I/II trial of sunitinib in 97 patients with imatinib-resistant/intolerant GIST, KIT mutation was reported to be a predictor of response, 58% with exon 9, 34% with exon 11, and 56% with wild type.[17]

Being able to predict the efficacy would be helpful for choosing treatment. Analysis of the KIT mutation status is desirable when IM is administered with the aim of reducing the extent of surgery.[15] The diagnostic rate of GIST with endoscopic ultrasound–guided fine needle aspiration and core needle biopsy is still 60% to 70%, which is inadequate, and various attempts have been made at improving that rate.[18] It was recently reported that endoscopic fine needle aspiration biopsy with Endosonopsy is useful.[19] This method was applied in the case reported here. It is desirable to diagnose GIST and analyze the KIT mutation status by some method.

Conclusion

The scope of invasiveness differs greatly as a function of the operative method used for GISTs of the duodenum, and NAC is considered an option with the objective of reduction surgery. Evaluating KIT exon mutation and predicting the effectiveness of NAC appear to be useful for determining the treatment policy

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