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A Giant Gastric Gastrointestinal Stromal Tumor Successfully Resected Following Neoadjuvant Treatment With Imatinib Mesylate

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Abstract. *Background: Neoadjuvant treatment with imatinib mesylate (IM) has not been established for gastrointestinal stromal tumor (GIST). A case of a giant gastric GIST that was radically resected following neoadjuvant therapy with IM is reported. Case Report: A 71-year-old woman with abdominal distension was referred to our hospital for treatment. Contrast-enhanced computed tomography showed a large (>30 cm), heterogeneous mass, with dilated vessels around the tumor. The diagnosis was a gastric GIST by endoscopic ultrasound-fine needle aspiration, and neoadjuvant therapy with 400 mg IM daily was started. Radical surgery was performed after 13 months. Since the tumor was not invasive, complete resection by partial gastrectomy was achieved without the need for combined resection of other organs. The patient remains alive without recurrence 12 months after surgery. Conclusion: A giant GIST, larger than 30 cm in size, is quite rare. Neoadjuvant IM treatment should be considered in the management of large GISTs.*

Gastrointestinal stromal tumor (GIST) is rare, although it is the most common mesenchymal tumor of the gastrointestinal tract, and its annual incidence is approximately 10 cases per million (1). Most GISTs harbor an activating mutation in KIT proto-oncogene receptor tyrosine kinase (KIT; 75-80%) or in platelet-derived growth factor receptor-α (*PDGFRA*; 5-10%) (2). Complete resection is the only potentially curative treatment for GIST. Fewer than half of all patients with GIST present with localized primary disease, and postoperative recurrence or metastasis is seen in 40-90% of all cases treated surgically (3-5). The most important factor for prolongation of survival in patients with GISTs is to improve the outcome of resection.

Imatinib mesylate (IM), a small-molecule inhibitor of oncoprotein KIT and PDGFRA, has been proven effective in clinical trials in patients with unresectable or metastatic GIST (6, 7). In randomized clinical trials, IM has also been reported to be effective as an adjuvant therapy for patients with a high risk of recurrence (8-10). However, the efficacy of neoadjuvant treatment with IM for resectable locally advanced GIST has not yet been established. Neoadjuvant treatment with IM is expected to induce significant reduction in tumor size, which may lead to an improved complete resection rate, avoidance of multiorgan resection, and a reduced risk of surgery. An unusual case of a very large gastric GIST that was radically resected without other organ resection and without tumor rupture following neoadjuvant therapy with IM is presented.

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

Case Report

A 71-year-old woman consulted a doctor with the chief complaint of abdominal distension. Contrast-enhanced computed tomography (CT) showed a large heterogeneous mass, and she was subsequently referred to our hospital for further treatment. The findings of the blood examination were normal, and tumor markers were not elevated. Abdominal CT showed a giant heterogeneous mass extending from the top of the left diaphragm to the pelvic cavity (about 40 cm in size) and dilated vessels around the tumor (Figure 1A). She was diagnosed with gastric GIST by endoscopic ultrasound-fine needle aspiration. It was considered that the risks of rupture of the tumor capsule and combined resection of other organs were high; therefore,

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neoadjuvant therapy with 400 mg IM daily was started. Thirteen months after the start of IM therapy, although the tumor size had been reduced by about 30% in the major axis and the dilated vessels had disappeared (Figure 1B and C), the last two consecutive CT examinations did not show further tumor shrinkage. Therefore, radical surgery involving total gastrectomy with splenectomy and partial resection of the diaphragm was planned. During laparotomy, the extramural tumor, whose root was only 3 cm, was found at the anterior wall of the upper stomach; therefore, partial resection was performed using a linear stapler (Figure 2). The tumor was not invasive; hence, the tumor was easily separated without rupture from the liver, spleen, and abdominal wall. Complete resection was performed with only partial resection of the stomach, without the need for combined resection of other organs.

The specimen was 30 cm in size, and the cut surface of the tumor showed it to be a yellow-gray solid mass with coagulative necrosis and a cavity (Figure 3). Histologically, cells in most sections of the tumor were fibrillated and vitrified, with bundled spindle-shaped cells. On immunohistochemistry, the tumor cells were positive for discovered on GIST1 (DOG1) and cluster of differentiation 34 (CD34), partially positive for KIT proto-oncogene receptor tyrosine kinase (KIT), and negative for S-100 protein, α-smooth muscle actin (α-SMA), and desmin. The number of mitotic cells was 0 in a high-power field (50×), and mindbomb E3 ubiquitin protein ligase 1 (MIB1) index was <1% (Figure 4).

The patient's postoperative course was uneventful, and 400 mg IM daily was resumed as adjuvant therapy on the sixth postoperative day. The patient is still alive without recurrence 12 months after surgery.

Discussion

An unusual case of a very large gastric GIST that responded to neoadjuvant therapy with IM, which led to safe and complete resection, was described. To the best of our knowledge, this is the first case of a giant GIST, larger than 30 cm, which underwent neoadjuvant IM effectively.

Neoadjuvant therapy with IM for large GISTs is expected to induce shrinkage of the tumor, which reduces the risks of tumor rupture, multiorgan resection, and R2 resection. Although to our knowledge, there are no randomized clinical trials of neoadjuvant treatment for large GISTs, a few retrospective studies and phase II clinical trials have demonstrated the benefit of neoadjuvant treatment with IM (11-15). An Asian multinational phase II study for 56patients with large gastric GISTs (≥10 cm) showed that the median shrinkage rate was 35%, the disease control rate was 100%, and the R0 resection rate was 91% (15). The Radiation Therapy Oncology Group 0132 phase II trial of IM for patients with locally advanced GIST (≥5 cm) reported that the disease control rate was 90%, and the R0 resection rate was 77% (13). These two phase II studies showed that neoadjuvant treatment with IM was tolerable and did not increase surgical complications. These studies did not include GISTs larger than 30 cm, but the present case also showed good tolerability and a good outcome, with complete resection without tumor rupture and no need for combined resection of other organs. Furthermore, in the present case, neoadjuvant treatment with IM induced not only tumor shrinkage, but also the disappearance of dilated vessels, which contributed to reduced bleeding. Thus, the present case suggests that neoadjuvant treatment with IM may be helpful in the management of large GISTs, even those larger than 30 cm.

The ideal duration of neoadjuvant treatment with IM remains controversial. It is considered that the optimal timing of surgery during IM is before secondary resistance or metastasis might develop, which is when the response to IM exhibits a plateau. Although reported disease control rates of neoadjuvant IM in clinical phase II trials were 90-100%, primary resistance has to be considered. Indeed, Navarrete et al. reported a case of rapid growth of a large gastric GIST despite neoadjuvant treatment with IM (16). Therefore, in the present case, the efficacy of IM was evaluated with an enhanced CT scan 1 month after the initiation of neoadjuvant treatment, and then follow-up CTs were performed every 3 months after the first evaluation showed the efficacy of IM. In the prospective studies of neoadjuvant IM for locally advanced GIST, the median time for the plateau response was about 6 months, and the median time of neoadjuvant IM administration was 6.5-8 months (15, 17). In the present case, because the tumor was very large, the aim was to reduce the tumor size as much as possible in order to be able to perform surgery safely and easily. To the best of our knowledge, there are limited data regarding how long neoadjuvant IM should be continued in order to achieve maximum reduction. Therefore, 10 months after starting neoadjuvant IM, the interval of evaluation with enhanced CT scan was changed from 3 months to 2 months because there was also the possibility of tumor growth, and surgery was considered when no further tumor shrinkage was observed between two consecutive evaluations. Consequently, radical surgery was performed 13 months after the start of neoadjuvant IM. The phase II study also indicated that neoadjuvant IM was discontinued within 1 week of surgery (15). On average, 75% of the dose of imatinib undergoes biotransformation. Imatinib has a terminal half-life of 19 h (range=14-23 h), while its main metabolite has a terminal half-life of 40 h (range=30-50 h) (18). It is within this context that IM was stopped 2 days before surgery in the present case.

A literature search using the PubMed database with the key words "gastrointestinal stromal tumor" and "large", "giant", or "huge" retrieved only three case reports of giant

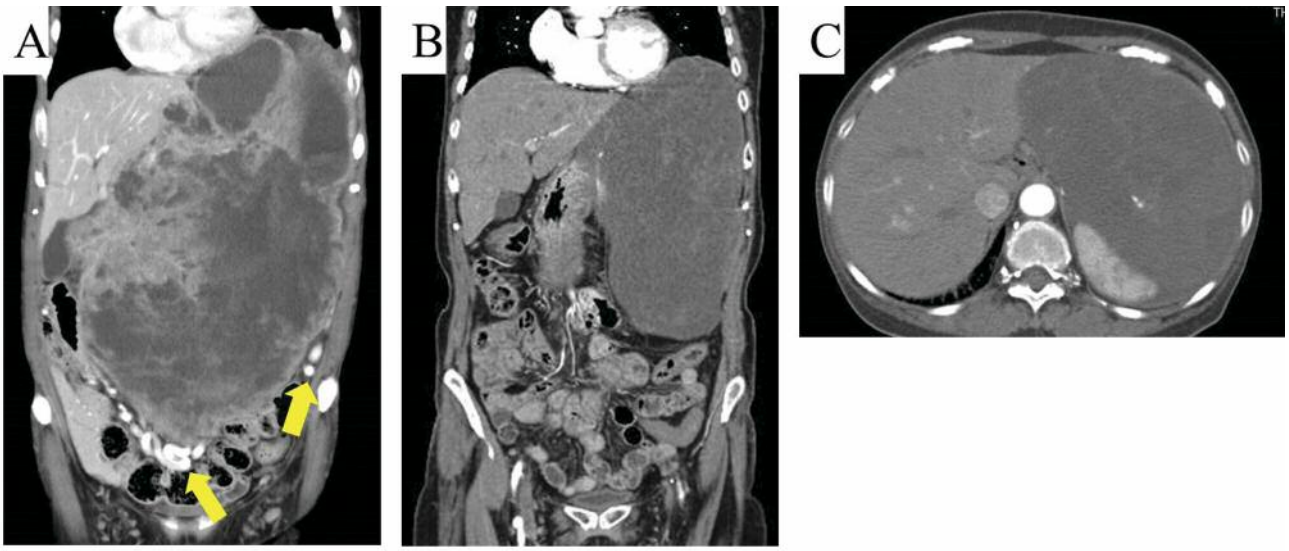

Figure 1. *Abdominal computed tomographic images before (A) and after (B and C) neoadjuvant treatment with imatinib mesylate (IM). A: A large heterogeneous mass was detected extending from the top of the left diaphragm into the pelvic cavity, with dilated vessels around the tumor (arrows). B, C: Thirteen months after the initiation of IM therapy, tumor size was reduced, and the dilated vessels had disappeared (B). Adhesion between the tumor and spleen was suspected (C).*

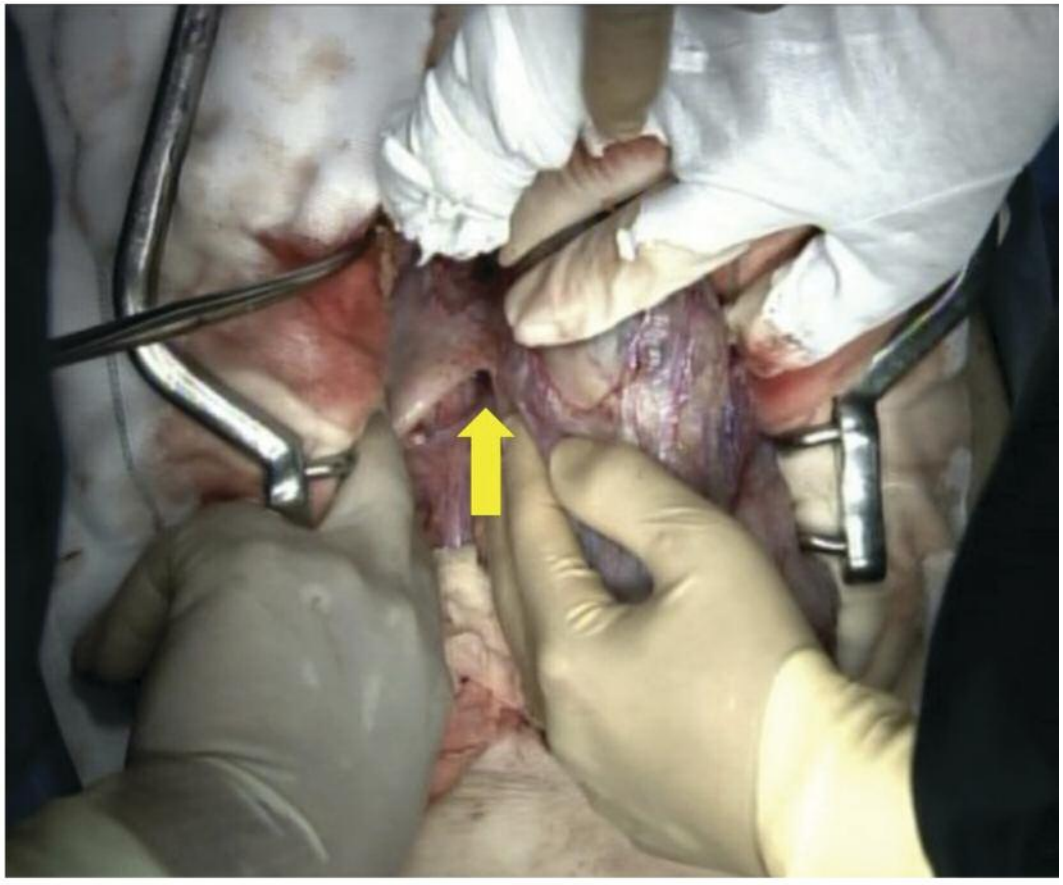

Figure 2. *Surgical view of the extramural tumor, whose root was only 3 cm, at the anterior wall of the upper stomach (arrow).*

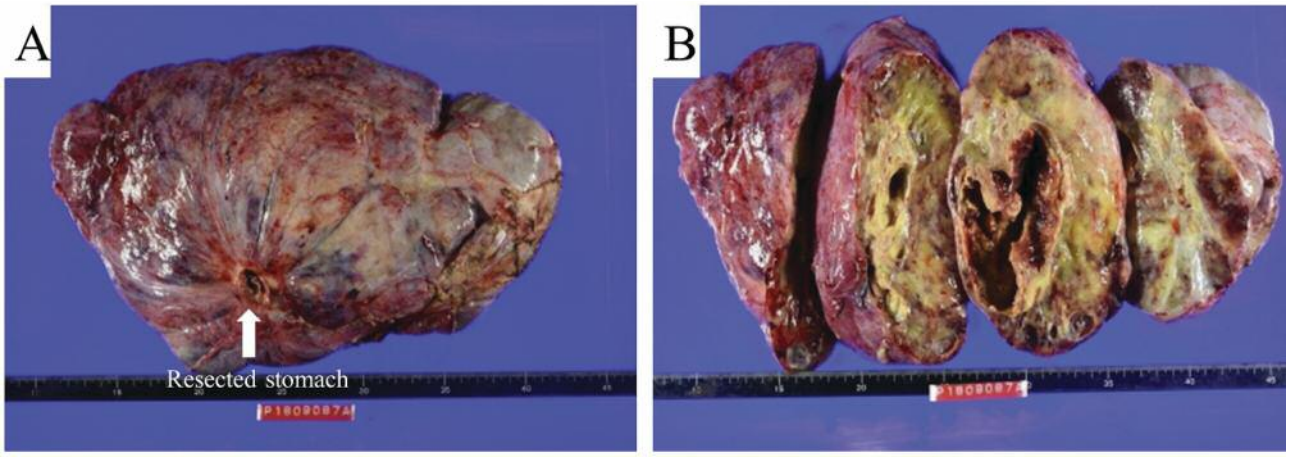

Figure 3. *Gross views of the resected specimen. The resected tumor was over 30 cm in size. B: The cut surface of the tumor showed it to be a yellow-gray solid mass with coagulative necrosis and a cavity.*

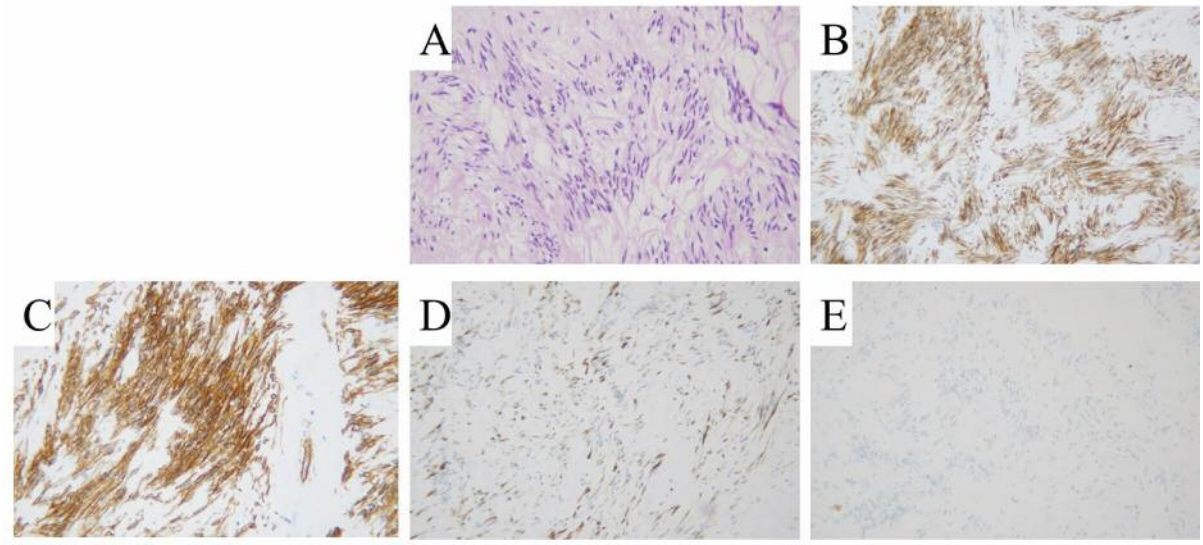

Figure 4. *Highlights of light microscopic images of the gastrointestinal stromal tumor (×100). A: Hematoxylin-eosin staining showing fibrillated and vitrified cells of the tumor, as well as bundled spindle-shaped cells. B-D: Immunochemical staining was positive for discovered on GIST1 (B) and cluster of differentiation 34 (C), and partially positive for KIT proto-oncogene receptor tyrosine kinase (KIT) (D). E: Ki-67 staining gave a proliferative index of <1%.*

GISTs, more than 30 cm in size, in the English literature (Table I) (19-21). In all four cases, including the present, GISTs were located at the stomach. Neoadjuvant treatment was performed only in the present case; therefore, the present case is the first to have undergone neoadjuvant IM for a GIST larger than 30 cm in size. In two cases (19, 20), emergency operations for gastrointestinal bleeding and bowel obstruction were performed, which may be one of the reasons why neoadjuvant treatment was not performed. In general, if the tumor is quite large, surgeons may consider that there is a high possibility of the need for combined resection of other organs. However, one case whose tumor was located at the posterior wall of the stomach required combined resection, whereas the other three cases whose tumors were located at the anterior wall of the stomach did not. It is known that GISTs generally grow expansively, not invasively. Indeed, in one case that required distal pancreatectomy-splenectomy, the resected specimen showed

Table I. *Published literature on gastrointestinal stromal tumor larger than 30 cm in size.*

Author (Ref)	Year	Location*	Age, years	Gender	Symptoms	Size (resected specimen) cm	Neoadjuvant treatment	Operation	Adjuvant treatment	Prognosis
Cruz *et al*. (19)	2008	Anterior wall	37	Male	Abdominal pain, nausea, vomiting	32	No	Subtotal gastrectomy	Yes	Alive without recurrence (12 months)
Cappellani *et al*. (20)	2013	Posterior wall	67	Male	Abdominal pain, nausea, vomiting, weight loss	37	No	Sleeve resection of stomach, distal pancreatectomy-splenectomy	Yes	Alive without recurrence (48 months)
Koyuncuer *et al*. (21)	2015	Anterior wall	43	Male	Abdominal pain	39	No	Partial gastrectomy	?	?
Our case	2018	Anterior wall	71	Female	Abdominal distension	30	Yes	Partial gastrectomy	Yes	Alive without recurrence (12 months)

*All cases were located on the stomach.

no infiltration of the tumor to the pancreas and spleen. We suppose that GISTs at the anterior wall of the stomach grow easily in the free abdominal space, whereas GISTs at the posterior wall of the stomach tend to adhere strongly to the organ surface because they grow in a narrow space in the omental bursa. From the above, it is possible that the need for combined resection of other organs may be lower in a case whose tumor is located at the anterior wall than at the posterior wall.

Although adjuvant therapy with IM for patients with GIST with a high risk of recurrence has been widely accepted (8-10), there is no evidence regarding adjuvant therapy for patients after radical resection following neoadjuvant treatment with IM. A phase III trial reported that 36 months of IM adjuvant therapy improved relapse-free survival and overall survival of patients with a high risk of GIST recurrence compared with only 12 months of treatment (9, 10). According to the results of that trial, in the phase II study to investigate the benefit of neoadjuvant treatment with IM for patients with large gastric GISTs, the study protocol recommended adjuvant IM for 3 years (15). The present case was also clearly classified as having a high risk of recurrence based on the modified Fletcher classification before treatment; therefore, adjuvant therapy with IM was planned for 36 months.

Conclusion

This rare case suggests that neoadjuvant IM treatment should be considered in the management of giant GISTs, even for tumors larger than 30 cm in size.

Conflicts of Interest

The Authors have no conflicts of interest to declare.

Authors' Contributions

Ryo Takahashi and Takahiro Toyokawa drafted the article. Mami Yoshii, Tatsuro Tamura, Hiroaki Tanaka, Shigeru Lee and Kazuya Muguruma participated in its design and coordination and helped to draft the article. Masakazu Yashiro and Masaichi Ohira contributed to critical revision. All Authors read and approved the final article.

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