A resectable case of gastrointestinal stromal tumor derived from the rectal wall after oral targeted molecular therapy with imatinib mesylate

Toshinari MURAMATSU, Tetsuji IIDA, Takeshi HIRASAWA, Kimitaka KIKUCHI, Isao YASUI, Masaru MURAKAMI, Eiko YAMASHITA[*1], Seiei YASUDA[*2], Hiroshi KAJIWARA[*3], Masanori YASUDA[*3], R. Yoshiyuki OSAMURA[*3] and Mikio MIKAMI

*Department of Obstetrics and Gynecology, [*1] Radiology, [*2] Surgery and [*3] Pathology, Tokai University School of Medicine*

(Received February 9, 2006; Accepted May 26, 2006)

We performed targeted molecular therapy in a patient with a non-resectable pelvic gastrointestinal stromal tumor (GIST). Imatinib mesylate was administered at 400-600 mg/day for 6 months, and the tumor became resectable. The patient was a 58-year-old female who visited a gynecologic hospital with the chief complaint of a swollen feeling in the lower abdomen. A pelvic tumor was found by imaging, and the patient was referred to our hospital. Laparotomy was performed, but it was found that the tumor arose from the intestinal serous membrane, rather than from the uterus, and complete excision was difficult. A portion of the tumor tissue was excised, and the abdomen was closed. GIST was diagnosed on postoperative pathological examination, and the tissue was positive for c-kit protein on immunostaining. The tumor had markedly shrunk after oral administration of imatinib mesylate for 6 months, and excision by laparotomy became possible.

Key words: gastrointestinal stromal tumor (GIST), gynecological tumor, imatinib mesylate

INTRODUCTION

Many cases of gastrointestinal stromal tumor (GIST) arise from the intestinal tract, but cases have recently been found in which the tumor contacts the gynecological organs at the boundary , and such tumors have been treated as gynecological tumors [1-4]. Expression of c-kit protein with tyrosine kinase activity is a characteristic of GIST, and the efficacy of targeted molecular therapy using imatinib mesylate has been reported for GIST [5]. Imatinib mesylate was initially reported to inhibit c-kit tyrosine kinase in chronic myeloid leukemia (CML) [6], and subsequently its effect on c-kit protein-positive GIST was shown and applied clinically [7]. Here, we report a patient in whom a large pelvic GIST was not resectable in the initial surgery, but then became resectable after administration of imatinib mesylate for 6 months.

CASE

Patient: 58-year-old female.
Chief complaint: A feeling of swelling in the abdomen.
Past medical history: Deep vein thrombosis of the lower limbs.
Present illness: The patient had a swollen feeling in the abdomen and distension for 3 months, and visited a gynecologic hospital. Abdominal ultrasonography and CT detected a huge pelvic tumor. Moreover, deep vein thrombosis of the lower limbs was found, and the patient was referred to our hospital for thorough examination. At admission, a giant tumor in the pelvic cavity was detected by abdominal MRI, and the tumor was considered to be due to degeneration of uterine myoma, based on the image (Figs. 1, A-1, 2). Deep vein thrombosis was detected by CT of the lower limbs and Doppler ultrasonography. No increases in tumor markers such as CA125, CA19-9, CEA and SCC were noted. An inferior vena cava filter was inserted before laparotomy to prevent postoperative thrombosis. Laparotomy was performed on the day after insertion of the filter, but during the procedure it became apparent that the giant pelvic tumor was associated with the small intestine, and excision was difficult. A portion of the tumor tissue was sampled, and the abdomen was closed. Histopathologically, outgrowth of round and spindle-shaped cells was noted in the excised tissue, and a diagnosis of gastrointestinal stromal tumor (GIST) was made based on irregular nuclear sizes and cell density. Since the tissue was positive for c-kit protein and strongly positive for CD34 on immunological staining, oral administration of 600 mg/day imatinib mesylate was initiated (Fig. 2). Since retention of pleural effusion and marked edema of the lower limbs occurred 2 months after initiation of imatinib mesylate administration, the dose was reduced to 400 mg/day, and a traditional medicine (Goreisan, Tsumura, Japan) was administered orally to improve edema. The course of the symptoms was observed, and pleural effusion and edema decreased after 2 weeks. After administration of imatinib mesylate for 6 months, imaging showed that the pelvic tumor had shrunk, and laparotomy was performed (Figs. 1, B-1, 2, and Fig. 3).

DISCUSSION

Gastrointestinal stromal tumor (GIST) mainly develops in the gastrointestinal tract, and is a Cajal interstitial cell-derived mesenchymal tumor expressing

Toshinari MURAMATSU, Department of Obstetrics and Gynecology, Tokai University School of Medicine, Shimokasuya 143, Isehara, Kanagawa 259-1143, Japan Tel: +81-463-93-1121 Fax: +81-463-91-4343 E-mail: mura-to@is.icc.u-tokai.ac.jp

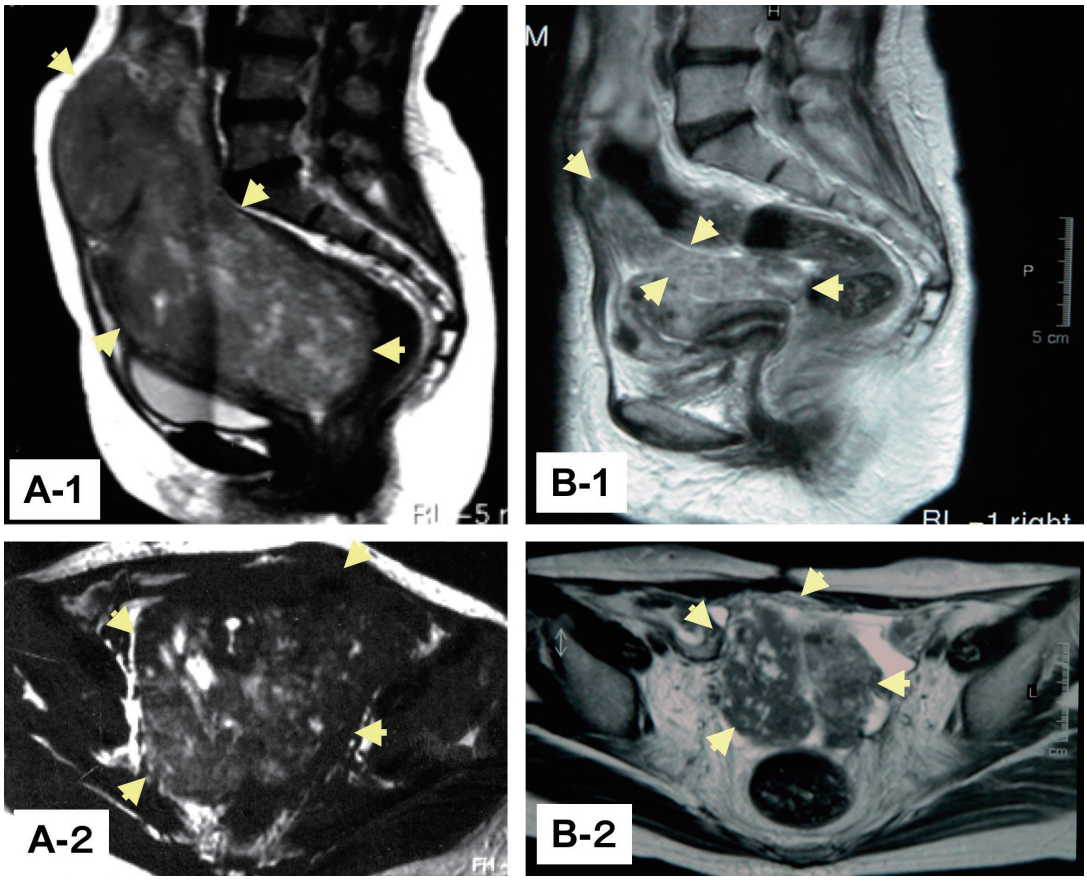

Fig. 1 Magnetic resonance imaging of the pre (A-1 longitudinal, 2 axial) - and post (B-1 longitudinal, 2 axial) - imatinib treatment. The pelvic tumor was good response after 6 months. (arrows)

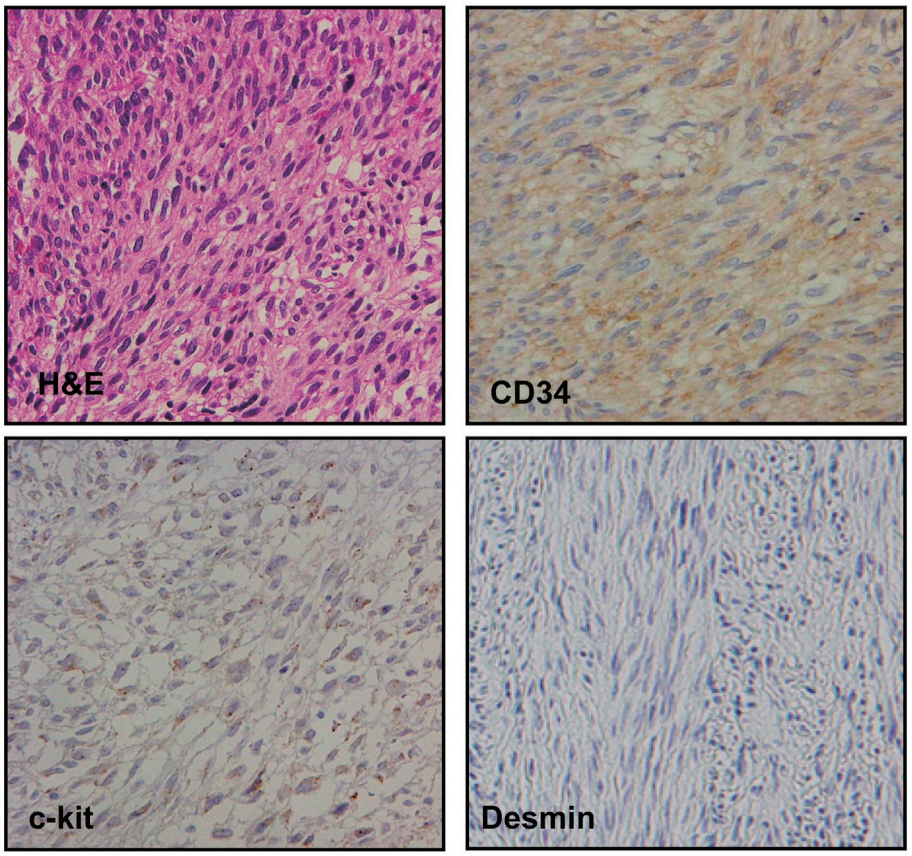

Fig. 2 H&E and Immunohistochemical analyses of GIST. The tumor showed a sporadic expression of c-Kit, a strong expression of CD34 and no expression of Desmin (×200)

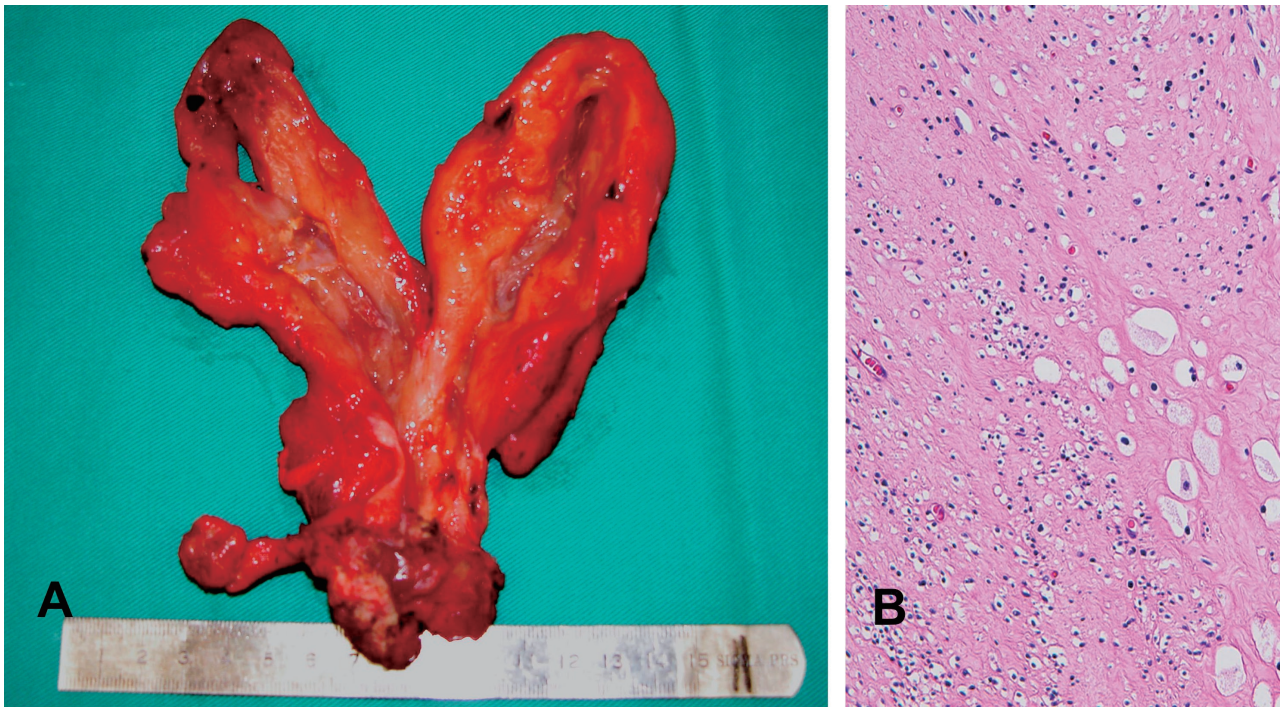

Fig. 3 The gross appearance of atrophic GIST (A) and pathological finding of necrotic degeneration (B) after imatinib treatment for 6 months.

c-kit protein with tyrosine kinase activity [5]. There are an increasing number of reports of cases of GIST originating in the small intestine and the lower digestive tract of the large intestine, in which the tumor contacts the uterus and ovaries at the boundary; these cases are initially discovered as pelvic tumors, but reported and treated as gynecological tumors [1-4]. Generally, 50-70% of all cases of GIST develop in the stomach, while tumors derived from the lower digestive tract are considered to account for about 7% of cases of GIST [8-10]. When GIST develops in a phyma-like form near the uterus, differentiation from degenerated uterine myoma and sarcoma using imaging is difficult in many cases, and MRI features of GIST are yet to be established in the literature [11]. In the current patient, T2-weighted MRI detected a phyma-like shadow with heterogeneous intensity in the pelvic cavity, and a giant uterine myoma was suspected. However, since a low-intensity region was also present, suggesting a gas around the tumor, a tumor derived from the intestinal membrane or a tumor involving the intestine was also considered.

In the current case, a giant tumor occupying the whole pelvic cavity was present at the time of the initial laparotomy, and the site of origin could not be identified because the small intestine surrounded the entire tumor. A portion of the tissue was excised and histologically investigated. As a result, the tumor was confirmed to be a c-kit protein (+) GIST, and based on this diagnosis we selected treatment with imatinib mesylate, which inhibits this protein. Imatinib mesylate was originally developed for targeted molecular therapy for chronic myeloid leukemia, but its effect on GIST has been reported and has attracted attention [12]. Administration of imatinib mesylate was initiated at 600 mg/day, but retention of pleural effusion and marked edema of the lower limbs developed 2 months after initiation of administration. The dose was reduced to 400 mg/day, and a traditional medicine (Goreisan, Tsumura, Japan) was administered to improve edema. This traditional medicine is unlikely to cause blood electrolyte disturbance, and retention of pleural effusion and edema of the lower limbs improved within 2 weeks. The imatinib mesylate was concomitantly administered thereafter, and the tumor markedly shrunk and became resectable by laparotomy.

Regarding the benign or malignant nature of a particular GIST, criteria based on tumor size, nuclear division, the presence or absence of necrosis, polymorphism, and cellular atypia have been investigated [13]. Tumor size and nuclear division are considered to be closely related as prognostic factors, and in the current case excision of the tumor was difficult because the tumor occupied the pelvic cavity, and the digestive tract surrounded the entire tumor. Since nuclear division of tumor cells was relatively weak on pathological examination and complete excision of the tumor was possible, a relatively good prognosis is expected, but careful follow-up is necessary in these cases, and attention to the possibility of recurrence is required.

REFERENCES

1) Nasu K, Ueda T, Kai S, *et al*. Gastrointestinal stromal tumor arising in the rectovaginal septum. Int J Gynecol Cancer 14: 373-377, 2004.
2) Carlomagno G, Beneduce P. A gastrointestinal stromal tumor (GIST) masquerading as an ovarian mass. World J Surg Oncol 13: 2-15, 2004.
3) Zighelboim I, Henao G, Kunda A, *et al*. Gastrointestinal stromal tumor presenting as a pelvic mass. Gynecol Oncol 91: 630-635, 2003.
4) Belics Z, Csapo Z, Szabo I, *et al*. Large gastrointestinal stromal tumor presenting as an ovarian tumor. A case report. J Reprod Med 48: 655-658, 2003.
5) Hirota S, Isozaki K, Nishida T, Kitamura Y. Effects of loss-of-

function and gain-of-function mutations of c-kit on the gastrointestinal tract. J Gastroenterol 35: 75-79, 2000.
6) Kantarjian H, Sawyers C, Hochhaus A, *et al*. Hematologic and cytogenetic responses to imatinb mesylate in chronic myelogenous leukemia. N Engl J Med 346: 645-652, 2002.
7) Hirota S, Isozaki K, Moriyama Y, *et al*. Gain-of-function mutations of c-kit in human gastrointestinal stromal tumors. Science 279: 577-580, 1998.
8) Miettinen M, Sarlomo-Rikala M, Lasota J. Gastrointestinal stromal tumours. Ann Chir Gynaecol 87: 278-281, 1998.
9) Fletcher CD, Berman JJ, Corless C, *et al*. Diagnosis of gastrointestinal stromal tumors: A consensus approach. Hum Pathol 33: 459-465, 2002.
10) Joensuu H, Fletcher C, Dimitrijevic S, *et al*. Management of malignant gastrointestinal stromal tumours. Lancet Oncol 3: 655-664, 2002.
11) Lau S, Tam KF, Kam CK, *et al*. Imaging of gastrointestinal stromal tumour (GIST). Clin Radiol 59: 487-498, 2004.
12) Steinert DM, McAuliffe JC, Trent JC. Imatinib mesylate in the treatment of gastrointestinal stromal tumour. Expert Opin Pharmacother 6: 105-13, 2005.
13) Miettinen M, Sobin LH, Lasota J. Gastrointestinal stromal tumors of the stomach: a clinicopathologic, immunohistochemical, and molecular genetic study of 1765 cases with long-term follow-up. Am J Surg Pathol 29: 52-68, 2005.