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A Patient with Recurrent Malignant Gastrointestinal Stromal Tumors Who Completely Responded to STI571

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Gastrointestinal stromal tumors (GIST) have been considered chemoresistant, but recent reports have demonstrated the efficacy of STI571 (imatinib), a tyrosine kinase inhibitor, for c-kit positive GIST. We describe our experience with a patient with radically unresectable recurrent gastric GIST which significantly responded to STI571. A 40-year-old man underwent cardiectomy due to cardial submucosal tumor, which was diagnosed as malignant GIST by histopathology. However, this tumor relapsed in the abdominal cavity 15 months after the first surgery and the recurrent tumor was resected again. The patient experienced five relapses in the abdominal cavity and liver in about 30 months, and every time surgical resection was performed. Finally this patient was admitted for the seventh time due to tumors developing in the mesenterium and remnant liver in October 2001. Encouraged by recent successful clinical reports of STI571 against GIST, STI571 twice daily at 400 mg/day was administered orally, and CT scan at week 6 showed disappearance of the tumor surrounding the aorta, regression of the metastatic liver tumor and the tumor beside the spleen. Abdominal CT scan after 4 months showed further regression of the tumors. Aspiration cytology of metastatic liver tumor did not show any distinctive tumor cells. STI571 is thought to be a possible standard treatment for patients with GIST.

Key words: stomach, GIST, STI571, imatinib, chemotherapy

Introduction

No effective chemotherapy has been available for gastrointestinal stromal tumors (GIST), tumors of the gastrointestinal tract originating from the stroma[1]. Recent reports demonstrating the efficacy of STI571 (imatinib), a tyrosine kinase inhibitor, for c-kit positive GIST, therefore appears to open a new phase in the treatment of GIST[2)3)]. We present here a patient with radically unresectable recurrent gastric GIST who significantly responded to STI571.

Case Report

At a regular medical check-up in December 1998, upper gastrointestinal X-ray revealed a protruded lesion in the upper stomach in a 40-year-old man. In January 1999, under a diagnosis of cardial submucosal tumor, cardial resection were performed. No residual tumor was observed by

macroscopic examination and the lesion was considered radically resected, and was diagnosed as malignant GIST with a maximum tumor dimension of 10.5 cm by postoperative histopathology. In March 2000, however, abdominal CT revealed a recurrent intraabdominal tumor and the tumor was resected. In August 2000, recurrent intraabdominal tumors appeared again and 7 tumors were resected (including partial splenectomy and partial excision of the small intestine). In December 2000, hepatic metastasis and other intraabdominal tumors were found and a partial hepatectomy at segment 6 was performed together with excision of 3 intraabdominal tumors. Chest CT performed in January 2001 revealed intramediastinal and intrathoracic tumors and attollens jejunum, and the tumors in the mediastinum and abdomen were excised. In May 2001, multiple liver metastases were diagnosed and the hepatic right lobe was excised. Abdominal CT performed in September 2001 revealed recurrence of the tumor in the remnant liver as well as intraabdominal tumors and the patient was admitted to the hospital for the seventh time in October 2001.

The results of hematology and blood chemistry showed no abnormalities. Abdominal CT scan revealed a metastatic focus about 4 cm in size in the remaining liver, a tumor 5 cm in size beside the spleen, and a tumor shadow surrounding the aorta (Fig. 1-A). Chest CT and pelvic CT scans also revealed a small tumor in the right thoracic cavity and a big tumor 2 cm in size in the pelvis.

On the basis of these results, diagnosis was made of recurrent gastric GIST which could not be radically resected. Administration of STI571 at 400 mg/day was started in October 2001. Due to NCI grade 2 nausea and vomiting, the dose was reduced to 300 mg/day in November 2001 and chemotherapy was continued. Abdominal CT scan at week 6 after the start of treatment showed disappearance of the tumor surrounding the aorta, regression of the liver metastasis and of the tumor beside the spleen, and necrosis inside the tumor (Fig. 1-B). abdominal CT scan at 4 months after the start of treatment showed further regression of the liver metastasis and the tu-

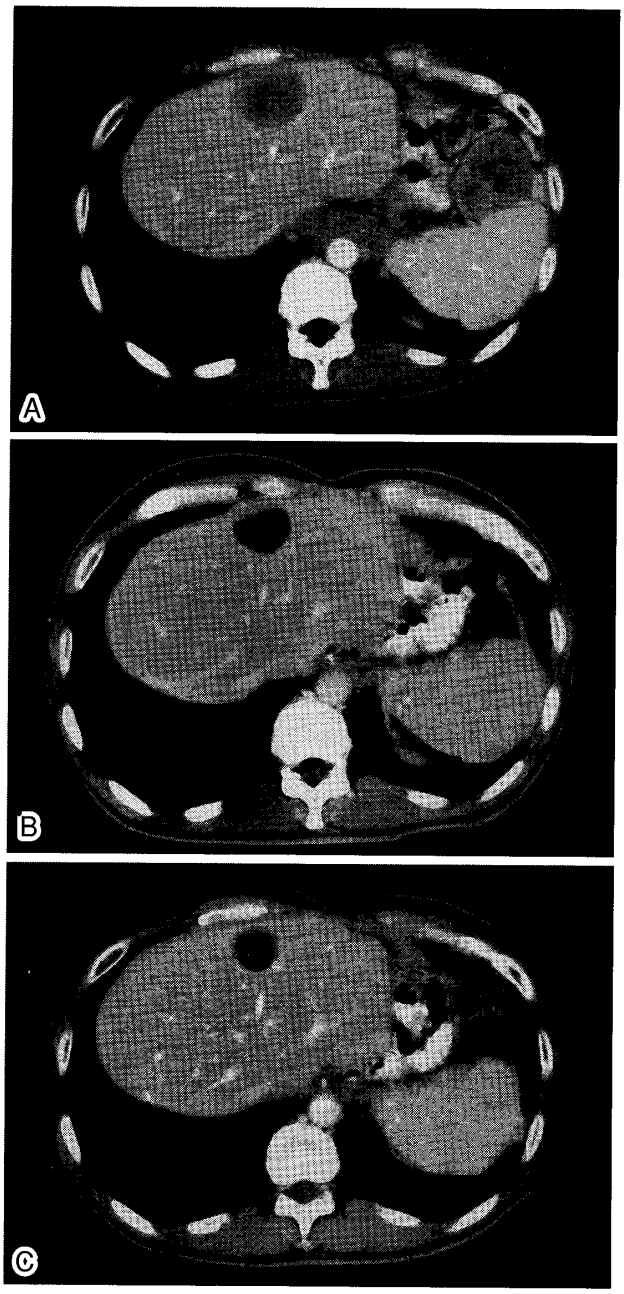

Fig. 1 CT
A: recurrent tumors in abdominal cavity, around the aorta and liver before STI571 administration.
B: after 6 weeks; no tumor was detected around the aorta and other tumors had cyst-like appearance.
C: after 4 months; no remarkable change from Fig. 1B.

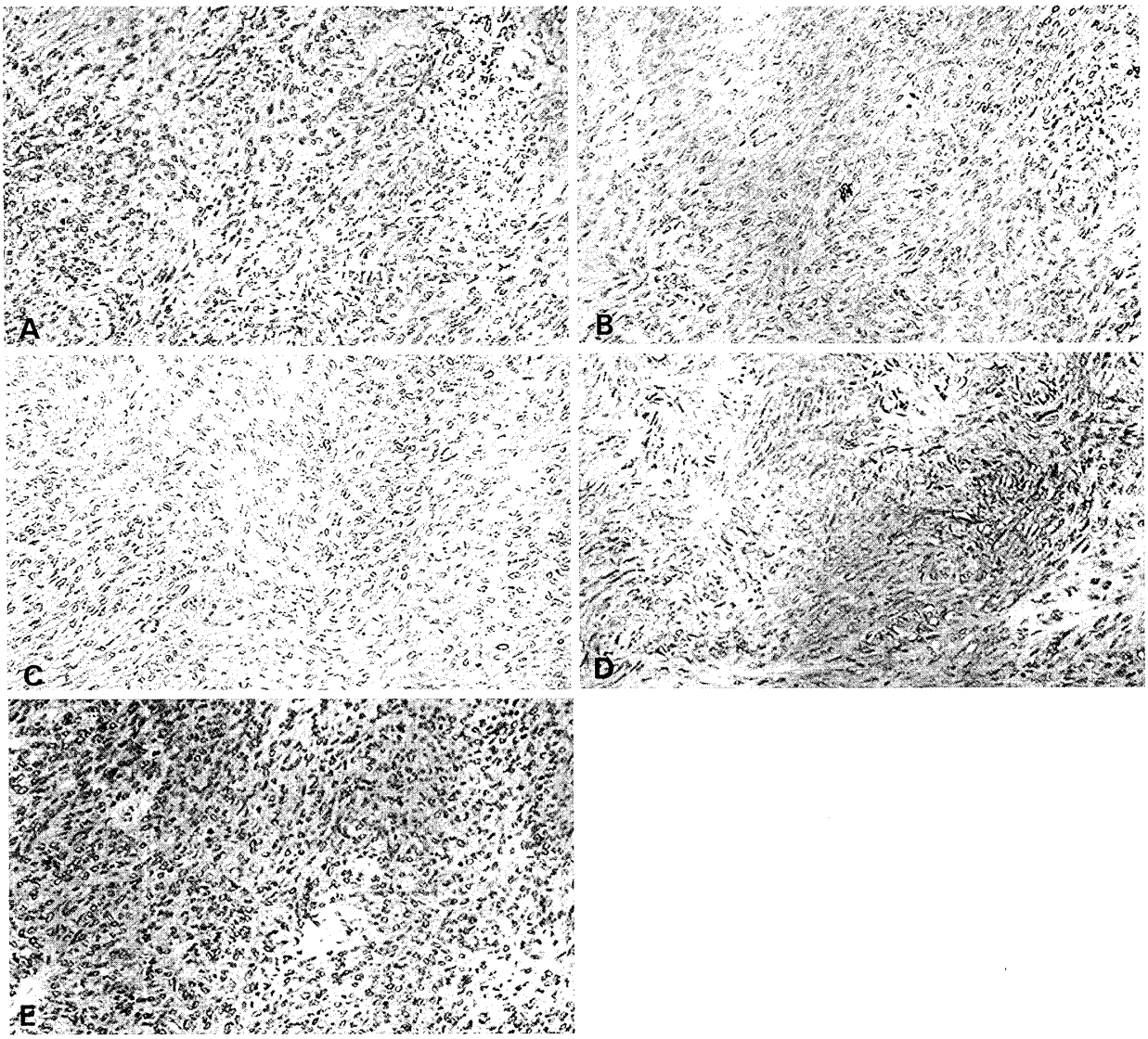

Fig. 2 Histological finding of primary gastric tumor (×100)
A: hematoxylin and eosine, B : α-SMA, C: S-100, D: CD34, E: C-kit.

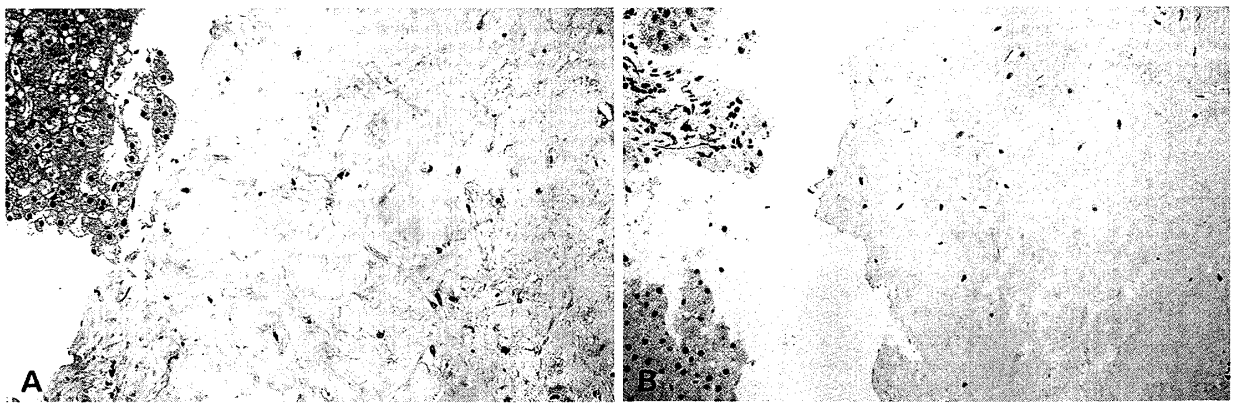

Fig. 3 Histological finding of liver metastasis (aspiration cytology, ×100)
A: myxoid degeneration, B: negative staining for c-kit.

Table Immunostaining

Antibody	Source	Dilution
Vimentin (monoclonal)	Dako, USA	1 : 200
α-SMA (monoclonal)	Dako, USA	1 : 300
CD34 (monoclonal)	Dako, USA	1 : 400
S-100 protein (polyclonal)	Dako, USA	1 : 50
C-kit protein (polyclonal)	Dako, USA	1 : 200

mor beside the spleen (Fig. 1-C) while chest CT scan and pelvic CT scan showed disappearance of the tumors. Because ultrasound-guided aspiration cytology of the liver metastasis did not show distinctive tumor cells, the dose of STI571 was reduced to 200 mg/day on March 8, 2002 and the therapy was being continued as of June 2002.

Histological findings: HE staining of the primary gastric tumor showed fascicular proliferation with spindle cells crossing orthogonally (Fig. 2-A). Immunostaining was performed with five antibodies (Table 1), and the results were as follows: vimentin positive, a-SMA negative (Fig. 2-B), S-100 protein negative (Fig. 2-C), CD34 positive (Fig. 2-D), and c-kit positive (Fig. 2-E). On the basis of these results, the lesion was diagnosed as GIST of uncommitted type. Because of numerous mitoses, high cell density and the presence of atypical nuclei, it was diagnosed as high-grade malignant tumor. The results of HE staining and immunostaining of specimens of metastasis foci after recurrence were the same as those of the primary foci.

Tissues obtained by aspiration cytology under ultrasonic microscopy of the metastasis foci of the remaining liver after 4 months were examined with HE staining and showed necrosis accompanied by myxomatous change (Fig. 3-A), and no positive cells were observed by c-kit staining (Fig. 3-B).

Discussion

Gastrointestinal primary mesenchymoma conventionally diagnosed by HE staining or silver impregnation as myogenic tumor or neurogenic tumor has come to be understood as a comprehensive GIST in a broad sense[4]. It is often diagnosed clinically as submucosal tumor and it is difficult to determine whether it is benign or malignant. Surgical excision is thus often selected as the first treatment when the lesion is of a certain size and malignancy cannot be denied. The treatment of malignant gastric GIST is often reported as favorable when complete resection is macroscopically confirmed, but there have been quite a few reports of postoperative recurrence of rather large GIST. Chemotherapy for GIST has been considered ineffective and no effective treatment other than surgical resection to the extent possible has been available for recurrent cases. Hirota et al[5] revealed c-kit mutagenicity in patients of GIST, and suggested that STI571, which possess an action for c-kit, is an effective chemotherapy for GIST. Its efficacy has been reported in many clinical cases[2)3)].

This patient underwent 6 surgical operations, including the initial surgery, during the 2 years and 6 months from January 1999 through June 2001. Although all the operations were considered radical resection by imaging and macroscopic observation, intraabdominal tumors and liver metastases recurred, and radical resection could not be achieved in the end. Until now, the prognosis in such cases was poor due to the lack of effective chemotherapy, but in the present case administration of STI571 led to complete remission and the patient is healthy at 6 months after treatment.

We believe that STI571 was effective in this patient because the tumor was uniform malignant GIST with positive immunostaining of c-kit with few variations.

Gastrointestinal symptoms such as nausea, vomiting and abdominal pain, eruption, muscle spasm and hematological abnormalities have

been reported as adverse reactions to STI571. This patient experienced severe nausea and vomiting and a dose of 400 mg/day, a standard dose for chronic myelocytic leukemia, was not tolerable. The treatment was continued by reducing the dose to 300 mg/day. No eruption or hematological abnormality was observed.

Given that the tissues obtained by aspiration cytology under ultrasonic microscopy of the liver metastasis after 6 weeks of STI571 administration did not show distinctive tumor cells or c-kit positive cells, the dose was reduced to 200 mg/day.

As stated above, the standard treatment for GIST is surgical excision but no effective therapy has been available for recurrences. For recurrent cases, we have performed excision of the metastatic lesion to the extent possible, as in this patient, but no patient has achieved complete remission so far. STI571 is orally bioavailable and can be used for outpatient treatment. We conclude that this drug could become a possible first choice treatment for patient with recurrent GIST.

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根治切除不能再発胃 malignant GIST に対し STI571 が著効した1例

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喜多村陽一（キタムラヨウイチ）・小熊　英俊（オグマヒデトシ）・笹川　剛（ササガワツヨシ）・林　和彦（ハヤシカズヒコ）・高崎　健（タカサキケン）

症例は40歳男性．胃 malignant GIST 原発巣切除術後再発をきたし，約2年6カ月の間に5回の再発巣切除を行った．しかし，再度再発し，骨盤から胸腔内まで多発転移巣を認め，腹部大動脈周囲を取り巻くように再発巣があることから根治切除不能と診断した．原発巣および切除転移巣の免疫染色において c-kit 陽性であったことからイマニチブの投与を開始した．6週間後の腹部 CT 検査において大動脈周囲転移巣の消失，肝転移巣，腹腔内転移巣の縮小，壊死化を認め，4カ月後の肝転移巣超音波下穿刺組織診において腫瘍細胞を認めなかった．これまで GIST に対する有効な化学療法はなかったがイマニチブの投与は再発 GIST の治療において第一選択となる可能性があると考えられた．