An Invasive Extragastrointestinal Stromal Tumor Curably Resected Following Imatinib Treatment

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ABSTRACT
Extragastrointestinal stromal tumors (EGISTs) are rare tumors located outside the gastrointestinal tract. While curable resection is accepted as a noninvasive EGIST treatment, the therapeutic strategy for invasive EGISTs has not yet been established. The present report is the first to show a case of invasive EGIST completely resected after downsizing the tumor with imatinib treatment.

A 69-year-old female had multiple masses adjacent to the stomach and ileocecum. The primary lesion measured 18 cm in size and had invaded the stomach, pancreas and liver. The histological findings of fine-needle aspiration samples revealed a proliferation of dysplastic spindle cells that exhibited immunoreactivity for anti-c-kit antibodies. The masses were therefore diagnosed as multiple GISTs with invasion to other organs, with origin difficult to determine at the time. Nineteen months after the imatinib treatment, the tumors were downsized and distinct from the stomach, pancreas and liver. Accordingly, the tumors were regarded to be EGISTs derived from the mesentery. Because they slightly regressed 26 months after treatment, surgery was applied to remove the EGISTs. The intraoperative findings showed no invasive signs, and the tumors were completely removed. The histological findings revealed the presence of dysplastic and c-kit-positive spindle cells in the tumor with an MIB-1 index of more than 5%, resulting in a final diagnosis of high-risk EGIST derived from the mesentery. No recurrence was detected for 16 months after resection.

In conclusion, preoperative treatment with imatinib followed by curable resection is a feasible option to cure invasive EGISTs.

Key words: extra-gastrointestinal stromal tumor – imatinib – surgery – pre-operative chemotherapy – conversion chemotherapy.

INTRODUCTION
Gastrointestinal stromal tumors (GISTs) are uncommon mesenchymal spindle-cell or epithelioid neoplasms that are generally located in the stomach or small bowel. Less than 5% of GISTs are located outside of the gastrointestinal tract in areas such as the mesentery, omentum and peritoneum (extragastrointestinal stromal tumors: EGISTs) [1, 2]. The widely accepted treatment for both GISTs and EGISTs is a complete resection when the tumors show no invasion or metastasis to other organs [1, 3, 4]. Recent advances in molecular-targeted treatment have led to the development of anti-tumor agents for GISTs, including imatinib and sunitinib, selective tyrosine kinase inhibitors that have been used to treat invasive and/or metastatic EGISTs [5-7]. The present report is the first to present a case of invasive EGIST completely resected after downsizing with imatinib mesylate treatment.

CASE REPORT
A 69-year-old female complained of abdominal fullness. Laboratory tests, including the levels of tumor markers, were unremarkable. A computed tomography (CT) scan revealed multiple masses around the stomach and ileocecum. The primary lesion measured 18 cm x 15 cm in size and exhibited initial enhancement of lobulated regions, followed by gradual enhancement of the entire mass with some heterogeneity. The margins between the mass and the adjacent organs, such as the
stomach, pancreas and liver were unclear (Fig. 1A). Magnetic resonance imaging (MRI) revealed an area of low signal intensity on T1-weighted images and high signal intensity on T2-weighted images in the primary mass, thus suggesting the presence of necrotic tissue in the mass (Fig. 1B). Fine-needle aspiration from the inside of the stomach was performed using endoscopic ultrasonography to obtain a histological sample. The histological findings of the FNA sample revealed proliferation of spindle cells with dysplastic changes in the nucleus (Fig. 2A). The cells showed immunoreactivity for anti-c-kit antibodies (Fig. 2B). Therefore, the primary mass was diagnosed to be multiple GIST invading the stomach, pancreas and liver. It was difficult to determine the origin of the tumors at the time, although the masses were thought to be invasive. Because the GISTs exhibited invasive signs and multiple lesions, a radical resection was not performed and 400 mg/day of imatinib mesylate was used to treat the patient at that time.

One week after treatment, the patient’s abdominal fullness was dramatically improved. CT images showed that the primary tumor had been downsized at six months from 18 cm to 10 cm and to 7 cm at 19 months after the treatment and that the margins of the tumor were distinct from the stomach, liver and pancreas at 19 months after treatment (Fig. 3A-C). Consequently, the administration of imatinib was found to be effective for the treatment of the tumor, and the primary tumor was regarded to be a mesenteric EGIST. However, the tumor regressed 26 months after treatment (Fig. 3D). Therefore, we decided to perform surgery to remove the multiple EGISTS. After obtaining written informed consent, the primary tumor and seven other lesions located in the mesentery were resected.

**Fig. 1.** CT and MRI findings. A) CT image showing multiple masses around the stomach and ileocecum (upper and lower). The primary lesion measured 18 cm x 15 cm in size and exhibited initial enhancement of lobulated regions in the arterial phase followed by gradual enhancement of the entire mass with some heterogeneity in the delayed equilibrium phase. The margins between the mass and other organs, including the stomach, liver (upper and lower) and pancreas (lower), were not clear (A). MRI revealed an area with low signal intensity on T1-weighted images (lower) and high signal intensity on T2-weighted images (upper) in the primary mass (B).

**Fig. 2.** Histological findings of the biopsy specimen. Histological findings of the biopsy specimen obtained from the primary lesion showing proliferation of spindle cells with dysplastic changes in the nucleus (A). Immunohistochemical staining showed that the tumor cells were positive for anti-c-kit antibodies (B).
The intraoperative findings showed the primary tumor to be 8 cm x 7 cm in size and connected, but not adherent, to organs such as the spleen and stomach. No lesions showed any invasive signs and were thus considered to be completely removed. The histological findings showed that degenerative tissue was present in many areas and that spindle cells with dysplastic changes in the nucleus remained in several parts of the tumors (Fig. 4A). Immunohistochemical staining showed a strong reactivity for anti-c-kit antibodies in the spindle cells (Fig. 4B). The MIB-1 index of the tumor cells was greater than 5% (Fig. 4C).

Taken together, the primary tumor was finally diagnosed to be a high-risk EGIST derived from the mesentery. Additional imatinib mesylate was administered, and no recurrent tumors were detected for 16 months after resection. Because no therapeutic strategy for invasive and/or metastatic EGIST after resection has yet been established, a long-term follow-up will be required to determine the optimal timing to stop the imatinib administration.

**DISCUSSION**

The current report presented a rare case of invasive EGIST that was curably resected after chemotherapy with imatinib mesylate. Although imatinib mesylate treatment is known to exhibit inhibitory effects on the progression of large and/or invasive EGISTs [6, 7], this report showed for the first time that preoperative treatment with imatinib mesylate followed by curable resection is a feasible option for curing invasive EGISTs. When the invasive findings of EGISTs are resolved by chemotherapy with imatinib or sunitinib treatment, surgical resection should be considered, even in cases of multiple EGISTs.

EGISTs are defined as soft tissue tumors derived from organs in the abdominal cavity, which is separate from the gastrointestinal tract, that are histologically similar to GISTs and positive for immunostaining of anti-kit antibodies [7].

**Fig. 3.** Downsizing of the primary lesion with imatinib treatment. Follow-up CT images showing that the primary lesion had been downsized from 18 cm (A) to 10 cm at six months (B) and to 7 cm at 19 months (C) after imatinib treatment. The margins of the tumor were distinct from the stomach, liver and pancreas at 19 months after treatment (C). At 26 months after treatment, the size of the primary tumor was slightly increased (D).

**Fig. 4.** Histological findings of the resected specimens. The primary lesion contained degenerative tissue in many parts, and spindle cells with dysplastic changes in the nucleus remained in several parts of the tumor (A). The spindle cells showed strong reactivity for anti-c-kit antibodies (B). The MIB-1 index of the tumor cells was greater than 5% (C).
The present patient exhibited a large tumor in the upper abdominal cavity that was histologically diagnosed as a GIST in the specimens obtained with FNA; however, the tumor was attached to the stomach, pancreas and liver. It was therefore difficult to diagnose the origin of the tumor. After imatinib mesylate treatment, the tumor was separated from these organs and was thereafter diagnosed as a mesenteric EGIST.

While complete resection is a widely accepted treatment method for EGISTs when the tumors show no invasion or metastasis to other organs [1, 3, 4], the therapeutic strategy for invasive and/or metastatic EGISTs has not yet been established. To date, chemotherapy with imatinib and sunitinib, selective tyrosine kinase inhibitors, is generally used to treat advanced EGISTs. The present report proposed a new strategy involving the combination of preoperative chemotherapy followed by surgical resection to cure invasive EGISTs. While the most effective period of imatinib mesylate for GISTs is from two to 12 months, the appropriate timing for combination therapy following resection is unknown. We decided to perform surgical resection 26 months after imatinib mesylate treatment in the present case, because the size of the primary tumor had regressed and the margin of the tumor thus became apparent.

CONCLUSION

Further analyses with a large number of EGISTs, similar to the recent case, are thus required to determine the indications and timing after surgical resection for combination therapy in patients with advanced EGISTs.

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