—**Report on Experiments and Clinical Cases**—

Gastrointestinal Stromal Tumor of the Stomach Diagnosed Preoperatively

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Abstract

A case of gastrointestinal stromal tumor (GIST) of the stomach is reported. GIST has been applied to gastrointestinal submucosal tumors mainly composed of spindle shaped cells that represent neither typical features of myogenic nor neurogenic tumors, and immunohistochemical studies are necessary for the diagnosis of GIST.

The patient was a 39-year-old man and was successfully diagnosed to be GIST (uncommitted type) preoperatively by immunohistochemical studies of biopsy specimens from an ulcerative submucosal tumor with bridging folds in the fundus, approximately 3.0 cm in size. Local excision of the stomach was performed. This is the 3 rd case of GIST with a preoperative diagnosis to appear in the literature in Japan.

For gastroenterological surgeons, it is critical to select the most suitable surgical procedure. In the present, because the number of papers reporting GIST of the stomach is small, it is impossible to review GIST clinicopathologically. We reviewed the surgical procedure for gastric leiomyosarcomas, because of including many cases with GIST in them. Therefore, we performed 54 cases of gastric GIST in the literature, compared with 92 cases of gastric leiomyosarcoma. As a result, it was thought that local excision for gastric GIST should be preferred.
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Keywords: GIST, submucosal tumor, preoperative diagnosis, surgical procedure, stomach

Introduction

It is becoming apparent that digestive tract submucosal tumors, which have been diagnosed so far as leiomyoma, leiomyosarcoma, schwannoma, or malignant schwannoma, include many gastrointestinal stromal tumors (GIST). Most GISTs are diagnosed histopathologically after resection. We report a case of GIST diagnosed preoperatively, and also review the surgical procedure for GIST of the stomach.

Case Report

The patient was a 39-year-old man with no specific complaint but only a past history of acute nephritis at age 13. In May 1997, at a medical examination, he was pointed out an abnormality by upper gastrointestinal series (GIS), and was also diagnosed by a medical doctor as having a cardiac ulcer to be treated. At the end of August 1998, a gastroendoscopy showed the ulcer had not healed and there was a small amount of

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gastric bleeding. Therefore, on September 5, 1998, the patient was referred to the Department of Internal Medicine. The outpatient section of the Department of Internal Medicine conducted an upper GIS and gastroendoscopy to detect a cardiac ulcer with a protruding lesion accompanied by a bridging fold; he was diagnosed as having a gastric submucosal tumor. Histological examination of the biopsy specimen confirmed the diagnosis of GIST. The patient was admitted to our department on November 4, 1998 for surgery.

On admission, his physical condition revealed a well nourished: height, 175 cm; weight, 70.5 kg; blood pressure, 120/72 mmHg; pulse, 82/min, regular; and no anemia or jaundice of the eyelid and conjunctiva. Physical examination of his chest and abdomen revealed no abnormalities and superficial lymph nodes were not palpable.

Laboratory findings on admission were as followed: hematology, biochemistry and urinalysis showed no abnormal values. Tumor markers were also within normal limits: CEA, 1.9 ng/ml; CA 19-9, 6 U/ml; IAP, 247 μg/ml; and neuron specific enolase (NSE), 5.6 ng/ml. Plain radiographs of his chest and abdomen were unremarkable.

Upper GIS (**Fig. 1**): Results disclosed a protruding lesion of approximately 3.0 cm in size, accompanied by central concavity near the greater curvature just under the esophago-gastric junction (EGJ). The mucous membrane of the central concavity was irregular, while the peripheral mucosa, including the adjacent zone, was smooth.

Gastroendoscopy (**Fig. 2**): There is a protruding lesion measuring 3 cm in size, accompanied by a central concavity with irregular ulceration, near the greater curvature of the fundus just under the EGJ. Since bridging folds were observed during endoscopy, we diagnosed a gastric submucosal tumor. But part of the folds terminated and were club-shaped, so carcinoma could not be ruled out. Therefore, we biopsied several sites including the folds. Despite an endoscopic ultrasound, the lesion located at a site hardly imaged and could not be seen fully. The biopsy results showed no change in the epithelium surrounding the folds (Group II). However, a biopsy at the ulcer border revealed obliterated lamina muscularis mucosae due to proliferation of spindle-shaped cells showing an interlacing pattern. Immunohistologic stainings (**Fig. 3**) revealed that the proliferating spindle cells were negative for α-smooth muscle actin (α-SMA) and S-100 protein, and positive for CD-34 and *c-kit*. The patient was diagnosed as having GIST of uncommitted type.

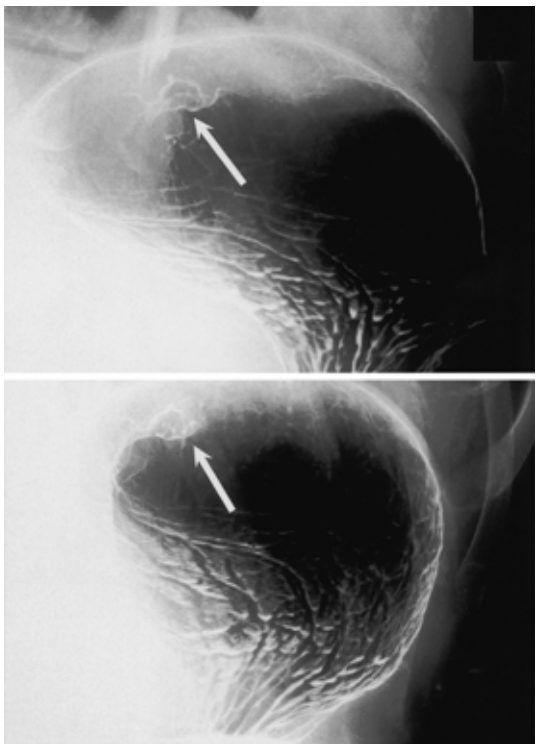

Fig. 1 Upper GI series showed an elevated lesion with central concavity (arrow) in the greater curvature of the fundus

Abdominal CT: We detected a protruding lesion of approximately 3.0 cm in diameter at the lumen of the gastric fundus but no regional lymph node enlargement or metastasis. We also noted a 0.8 cm cyst and a 1.0 cm hemangioma in the liver at S 8 and S 6, respectively.

Based on these findings, the patient was judged to have developed an endogastric submucosal tumor at the cardiac region, and was histologically diagnosed with GIST, uncommitted type, and low grade malignancy, with a size of 3.0 cm. CT revealed no evidence of metastases to the lung, liver or peritoneum nor direct invasion to other organs. Therefore, a local excision was scheduled and done on November 13, 1998.

Operative findings: Laparotomy was carried out by epigastric transverse incision. No metastasis of the liver or peritoneum was found. Since the tumor was slightly toward the posterior wall of the cardiac

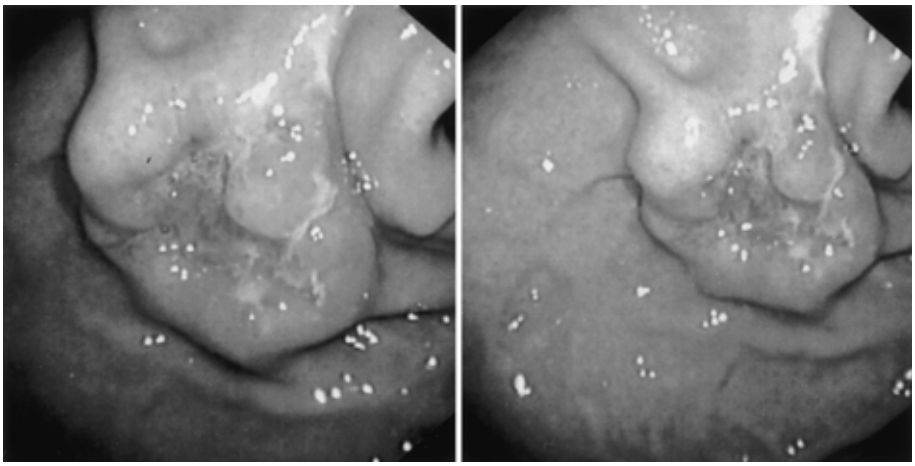

Fig. 2 Endoscopic findings showed an ulcer on a submucosal tumor measuring approximately 30 cm in diameter with bridging folds in the fundus

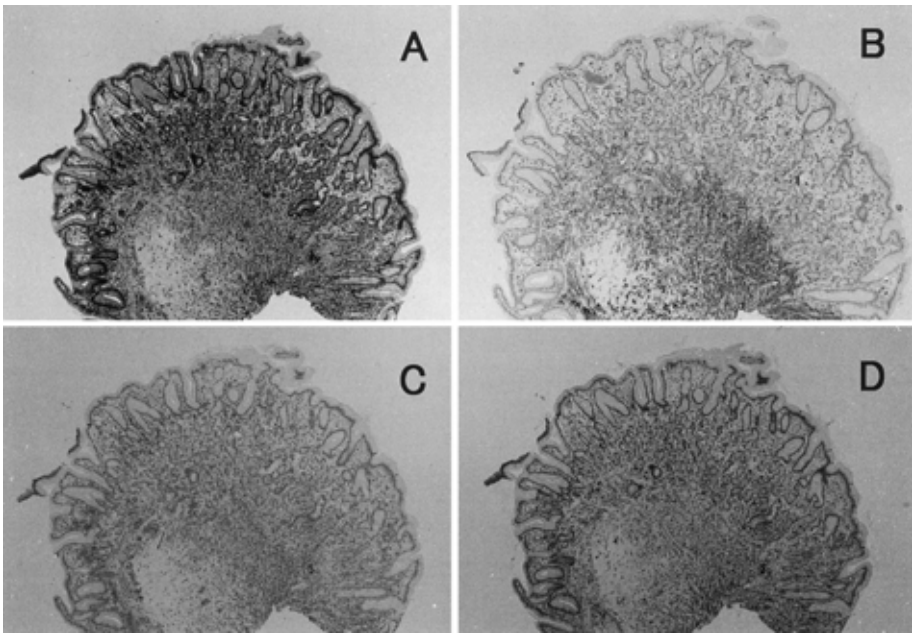

Fig. 3 Histological findings of biopsied specimen
A: H.E.(×10): Spindle shaped cell proliferation mainly in the submucosa with dispersed lamina muscularis mucosae
B: CD 34 (×10): Positive findings in neoplastic cells and capillary endothelial cells
C: α-SMA (×10): Negative (positive: lamina muscularis mucosae)
D: S-100 (×10): Negative

greater curvature, just under the EGJ, the greater curvature was mobilized by clamping and severing short gastric vessels. There was no invasion to the serosal membrane, or lymph node enlargement in Nos. 2, or Nos. 1, 3, 4–7 and 10. Therefore, a local excision was performed, and the No. 2 lymph nodes were dissected for test sample.

Pathologic examination: Grossly, the resected lesion was a submucosal tumor measuring 2.0×3.0 cm in size with an ulcer on the mucosa. The cut surface was homogeneous, milky white with a well defined boundary. Histological studies revealed a solid tumor composed of spindle cells with fascicular and interlacing patterns at the proper muscle layer extending to the submucosal layer, and the cellularity was high with a frequent mitotic figure in part. The No. 2 lymph nodes

showed no metastasis (0/4). Immunohistochemical studies (**Fig. 4**) resulted in strongly positive with vimentin, CD-34 and *c-kit*, and negative with α-SMA, desmin, NSE and S-100 protein. All the results corresponded to those obtained at biopsy. These findings indicated that the tumor cells were composed of immature mesenchymal cells without muscular and neural differentiation or maturation. The patient was diagnosed to have GIST, uncommitted type with low grade malignancy. At present, 2 years and 5 months postoperatively, the patient is doing well without recurrence and is being followed as an outpatient.

Discussion

Gastric submucosal tumor is a collective term covering situations where the main lesion is under the mucosa; a hemispherical or spherical lesion protrudes into the gastric lumen; and the lesion is classified into myogenic, neurogenic, fat cell-derived, or fibroblast-derived types and so on[1]. Naturally, GIST is now classified as a submucosal digestive tract tumor. With the progress of immunohistochemistry, some tumors did not correspond to the classification. As a result, the concept of GIST was proposed[2]. Historically, myogenic and neurogenic tumors were those mainly composed of spindle cells, and most of them could hardly be differentiated under HE staining. But after the development of immunohistochemical stain method using a neural marker, S-100 protein, a muscular markers, α-SMA and desmin, the differentiation of myogenic and neurogenic tumors became easier. This also resulted in the finding of a new tumor type that could not be classified definitely into the myogenic or neurogenic type[3]. In 1995, Rosai J.[2] reported, in Ackerman's Surgical Pathology, 4 GIST types: 1) smooth muscle, 2) neural, 3) combined smooth muscle-neural, and 4) uncommitted types. This was an initial and comprehensive definition of GIST. There are other reports defining GIST. For example, Miettinen M. et al[4] defined GIST as neoplasms without typically myogenic or neurogenic differentiation or with uncommitted type alone; another report[5] defined GIST as a tumor originating from interstitial cells of Cajal (ICC), a pacemaker cell in the intestinal neuroplexus in the digestive tract; and an other report proposed a new term such as gastrointestinal pacemaker cell tumor (GIPACT)[6]. Thus, while the definition is not fully es-

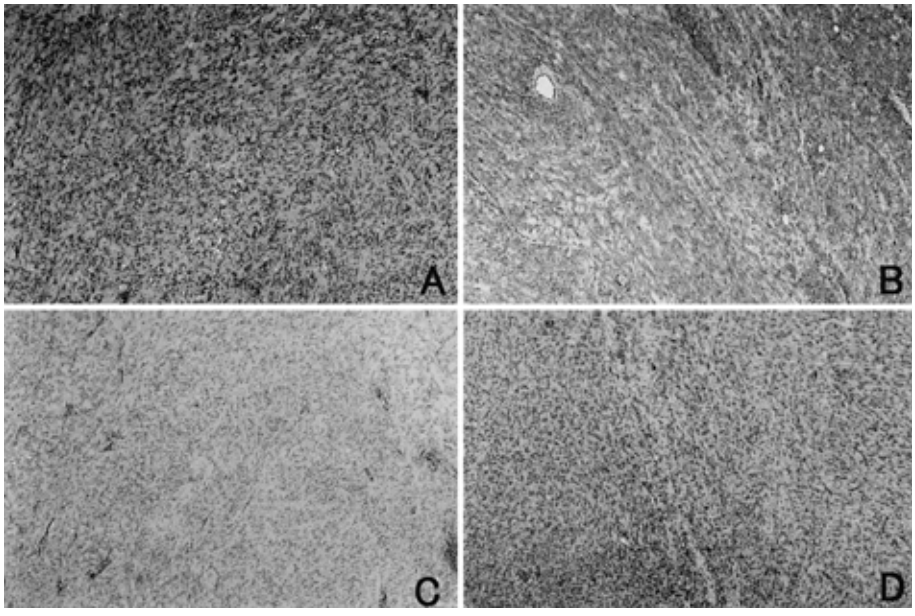

Fig. 4 Histological findings of resected specimen
A: H.E. (×20): Spindle shaped cells arranged in fascicular and interlacing patterns, and cellularity is high
B: CD 34 (×20): Diffusely and intensely positive in spindle-shaped neoplastic cells
C: α-SMA (×20): Negative
D: S-100 (×20): Negative

tablished, it is at least acceptable to define GIST for the uncommitted type.

Most submucosal tumors of the digestive tract are diagnosed postoperatively. Furthermore, to establish a diagnosis of GIST, immunohistopathologic examination is essential; GIST can not be diagnosed by routine HE staining alone. Thus, it is far more difficult to diagnose GIST preoperatively. No specific procedure has been devised for the preoperative diagnosis of GIST of the stomach, which has been done using the same method as for gastric submucosal tumors. Upper GIS, gastroendoscopy and biopsy are commonly employed to diagnose GIST, occasionally together with CT and endosonography. All this rarely results in a definitive diagnosis of GIST preoperatively. It is difficult to collect submucosal tumor tissue with biopsy under routine endoscopy because of its location in the submucosal layer. To cope with this, procedures include high frequency current, large biopsy forceps, laser coagulation, or pure ethanol method[1]. They sometimes have complications such as hemorrhage or thermal denaturation of the tissues, and result in a low diagnostic ratio. Fortunately, our patient had only a 3.0 cm lesion with an ulcer, and did not develop scarring. And, assisted by the Pathology Department, it was possible to make a diagnosis preoperatively.

In Japan, the concept of GIST has been spreading since about 1996, and many reports have been published since 1998. In our review of the literature (JMEDICINE, 1991～1999), our patient was the 3 rd case to be diagnosed with GIST preoperatively. The other cases[7,8], in whom lesions originated in the stomach and were accompanied by an ulcer, were diagnosed preoperatively using immunologic staining. GIST originating in the stomach has been reported in Japan in 13 communications[7-19] involving 16 patients, these numbers are too small for a clinicopathologic review. However, for gastroenterological surgeons, it is critical to select the most suitable operative procedures for GIST. We investigated 54 patients in total (**Table 1**), including 38 patients in whom operative procedures have been described in Journals of Medical Associations, together with the 16 patients mentioned above. Three (5.6%) patients had a tumor enucleation, 26 (48.1%) had a local excision, 9 (16.7%) had a total gastrectomy and 15 (27.8%) had a partial gastrectomy (6 (11.1%) had a cardio resection, and 9 (16.7%) had a distal resection).

Table 1 Comparison of surgical procedure between GIST and Leiomyosarcoma of the stomach

	GIST (%) n=54	Leiomyosarcoma (%) n=92
Tumor-gastric anasto.	1 (**1.8**)	0 (**0**)
Tumor enucleation	3 (**5.6**)	1 (**1.1**)
Lacal excision	26 (**48.1**)	44 (**47.8**)
Total gastrectomy	9 (**16.7**)	4 (**4.3**)
Partial gastrectomy	15 (**27.8**)	43 (**46.8**)
Cardio resection	6 (11.1)	19 (20.7)
Distal resection	9 (16.7)	24 (26.1)

The authors[20] previously reported that many GIST patients were included among those with leiomyoma or leiomyosarcoma, diagnosed as myogenic or neurogenic tumor. Gastric leiomyoma is generally treated by tumor enucleation or local excision. However, because leiomyosarcomas are occasionally less than 5 cm in diameter, tumor enucleation should be avoided. Although gastric leiomyosarcoma is a malignant tumor, local excision is adopted for gastric leiomyosarcoma since hematogeneous metastasis and peritoneal dissemination are more common and lymph node metastasis rarely develops. Lymph node dissection is unlikely to affect prognosis[21,22]. Similarly, patients with a neurogenic tumor have mostly hematogeneous metastasis and rarely lymphogeneous metastasis resulting in no significance of systemic lymph node dissection. Therefore, local excision is recommended for the patients [23].

Leiomyosarcoma is reported most frequently in both myogenic and neurogenic tumors of the stomach, so we discussed GIST in comparison with leiomyosarcoma. We employed a control group of 92 patients with gastric leiomyosarcoma in 3 reports[21,22,24] from the facilities to understand these characteristics sufficiently, and comparatively assessed the operative procedures for 54 patients with GIST (**Table 1**). There was no difference between GIST and leiomyosarcoma in local excisions. Total gastrectomy was more frequently employed in patients with GIST than in those with leiomyosarcoma. Partial gastrectomy was conducted in lesser numbers of patients with GIST than with leiomyosarcoma. Almost all of the 146

patients performed the operation under a diagnosis of gastric submucosal tumor or of suspected gastric leiomyosarcoma. The reports of gastric GIST described that many cases underwent lymphnodes dissection. In the group of gastric GIST, this may have resulted in many patients having undergone total gastrectomy because the surgeons reporting gastric GIST were not well aware of these characteristics of gastric leiomyosarcoma. Consequently, at present, it is thought that operative procedures for myogenic and neurogenic tumors should also be applied for GIST. Local excision for gastric GIST should be preferred, although total or partial gastrectomy is indicated in patients with a large tumor accompanied by direct invasion of other organs.

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