CASE REPORT

# Giant gastrointestinal stromal tumor, associated with esophageal hiatus hernia

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**Abstract : An 85-year-old woman was admitted to our hospital because of vomiting. An upper gastrointestinal series what showed a large esophageal hiatus hernia, suggesting an association with extrinsic pressure in the middle portion of the stomach. An upper gastrointestinal endoscopic examination showed severe esophagitis and a prominent narrowing in the middle portion of the stomach, however, it showed normal gastric mucosa findings. CT and MRI revealed a large tumor extending from the region of the lower chest to the upper abdomen. From these findings, the tumor was diagnosed as gastrointestinal stromal tumor (GIST), which arose from the gastric wall and complicated with an esophageal hiatus hernia. We performed a laparotomy, however, the tumor showed severe invasion to the circumferential organs. Therefore, we abandoned the excision of the tumor. Histologically, the tumor was composed of spindle shaped cells with marked nuclear atypia and prominent mitosis. The tumor cells were strongly positive for CD34 and c-kit by immunohistochemical examination. From these findings, the tumor was definitely diagnosed as a malignant GIST. As palliative treatment, we implanted a self-expandable metallic stent in the narrow segment of the stomach. The patient could eat solid food and was discharged. In the treatment of esophageal hiatus hernia, the rare association of GIST should be considered.**
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***Keywords*** **:** *gastrointestinal stromal tumor, esophageal hiatus hernia, self-expandable metallic stent*

## INTRODUCTION

Gastrointestinal stromal tumor (GIST) constitutes the largest category of primary non-epithelial neoplasms of the stomach and the intestine. They arise from cells, located in the wall of the gastrointestinal organs and show marked variability in their differentiation pathways (1). In this report, we will report the case of a woman with giant GIST originating from the stomach wall, and associated with an esophageal hiatus hernia. We also report the beneficial effect of a self-expandable metallic stent for palliative treatment against stricture due to non-curable GIST. No autopsy was performed.

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## CASE REPORT

An 85-year-old woman with a chief complaint of vomiting was referred to our hospital on December, 22, 2000. She had complained of heartburn after meals for the 4 months prior to admission. She visited a local hospital, and an upper gastrointestianl endoscopic examination showed an esophageal hiatus hernia and atrophic gastritis. She had complained frequently of epigastralgia and appetite loss for the 3 months prior to admission, and these symptoms had gradually increased. She had no history of other severe diseases. On admission, the patient's general condition was stable, except for slight anemia. The heart sound was clear, and the respiratory sound was normal. The other physical examinations showed no abnormalities. She was 138.5 cm tall and her body weight was 36.9 kg. Her blood pressure was 142/80 mmHg, pulse rate was 72 beats per minute and regular, although its tonus was dull, the respiration was 13 per minute, and her body temperature was 36.2°C. Laboratory studies revealed : White blood cell count, 5,500 cells/$mm^3$ ; Hematocrit, 30.1% ; Hemoglobin, 9.8 mg/dl ; Platelets count, 22.9×$10^4$/$mm^3$, Total protein, 6.0 g/dl ; Albumin, 3.4g/dl ; Total bilirubin, 0.26 mg/dl ; GOT, 20 IU/liter ; GPT, 19 IU/liter ; Alp, 279 IU/liter ; LDH, 329 IU/liter ; Choline esterase, 192 IU/liter ; Na, 141 mEq/liter, K, 4.00 mEq/liter, Cl, 104 mEq/liter ; BUN, 19.2 mg/dl ; Creatinine, 0.57 mg/dl ; UA, 2.8 mg/dl ; Serum-amylase, 77.0 IU/liter ; Total choresterol, 158 mg/dl ; Triglyceride, 120 mg/dl ; Bleeding time, 1 minute ; Prothorombin activity 93% ; APTT, 30.8 minute ; Hepplastin tast, 122.0% ; CRP, 0.13 mg/dl ; CEA, less than 0.5 mg/dl (within normal limit) ; NSE, 6.3 ng/ml (within the normal range). An electrocardiogram showed atrial fibrillation. Respiratory function, Vital capacity, 1.43 L ; %VC, 80% ; $FEV_{1.0\%}$, 80.41%. A chest X-ray examination showed no sign of a tumor or other disorders. An upper gastrointestinal series showed a large esophageal hiatus hernia, which also suggested an association with extrinsic pressure in the middle portion of the stomach (Fig. 1), however, the passage of the contrast medium was seen to be normal from the lower body of the stomach to the duodenum (Fig. 1). An upper gastrointestinal endoscopic examination showed marked flexion at the middle esophageal portion, in which the redness of the mucosa was marked, suggesting severe esophagitis. From the middle to the lower portion of the body of the stomach, a prominent narrowing was found, however, no other disorders, such as erosion and ulcers were seen in the gastric mucosa. On computed tomography (CT), a soft tissue mass, 8 by 9 cm, was seen (Fig. 2). This tumor was heterogenous on the contrast-enhanced scan. On the magnetic resonance image (MRI), the T 1-weighted image showed iso-intensity (Fig. 3A), and the T 2-weighted image showed hyper-intensity (Fig. 3B). The MRI image strongly suggested invasion of the tumor into the aorta and the esophageal hiatus (Fig. 3 A, B). Endoscopic ultrasonography

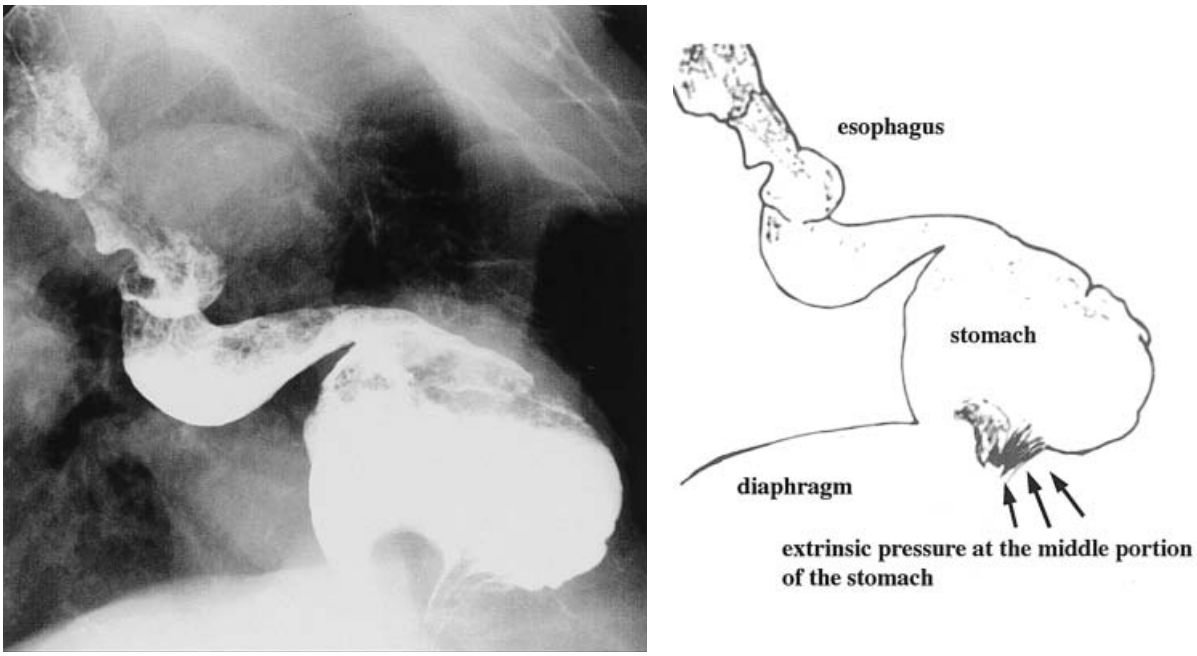


Fig. 1. Upper gastrointestinal view. Arrows show the site of extrinsic pressure in the middle portion of the stomach.

(7.5 Mz EUS) suggested that this tumor originated from the wall of the stomach and extended extra-luminally. Based on these findings, we diagnosed the tumor as GIST, strongly suggesting malignancy. On 17, January, 2001, a laparotomy was performed under general anesthesia with an upper median incision and a left oblique abdominal incision. A small amount of bloody ascites was detected. In the intra-peritoneal cavity and organs, there was no finding of a mass, suggesting metastases. The tumor showed an abundance of vessels, located from the anterior wall of the upper body of the stomach to the esophageal hiatus, extending beyond the hiatus into the posterior mediastinum. The tumor markedly invaded the bilateral curus of the diaphraguma, the retro-peritoneum, the lesser omentum, and bled easily during the operative procedures (Fig. 4). We abandened the excision of the tumor, and performed only a biopsy for histological analysis, considering the patient's condition. In the histological findings of the excised specimen with hematoxylin-eosin-staining, the tumor contained uniform spindle cells, arranged into a follicular growth pattern, including the foci of dense cellularity (Fig. 5A). The mitotic response was greater than 10 mitotic figures per 50 HPF (Fig. 5B). Immunohistochemical staining was negative for S100 protein (Fig. 6A) and α-SMA (Fig. 6B), but, positive for vimentin (Fug. 6C), CD34 (Fig. 6D), and c-kit (Fig. 6E). From these findings, the tumor was diagnosed as a malignant gastrointestinal stromal tumor. The patient suffered post-operatively from cardiac failure and lung congestion, and she was treated with digitalis and gradually recovered. On day 21 post-operatively, she was implanted with a self expandable metallic stent (SEMS), non-covered Ultraflex type (MicrovasiveR ; distal release system ;

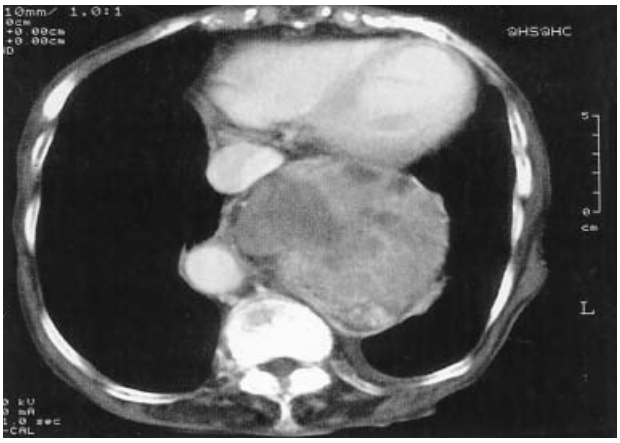

Fig. 2. The findings of enhanced computed tomography.

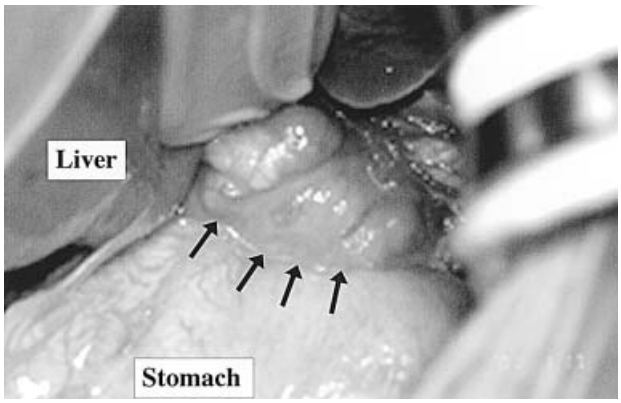


Fig. 4. The laparotomy findings. Black arrows show the distal edge of the tumor arising from the anterior wall of the stomach.

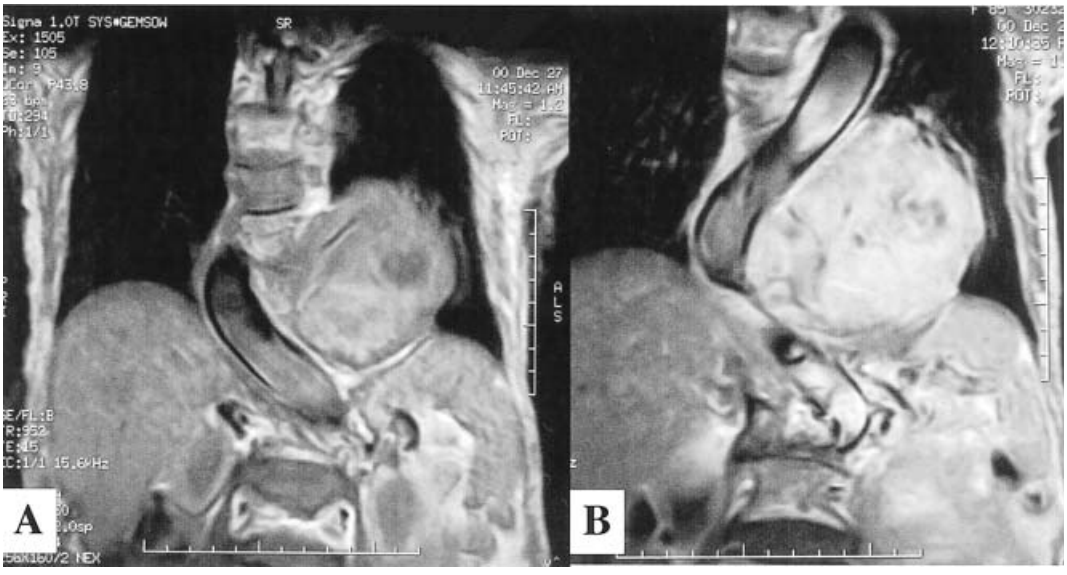


Fig. 3. The findings of the magnetic resonant imaging. Fig. 3A is the T1-weighted image and Fig. 3B is the T2-weighted image.

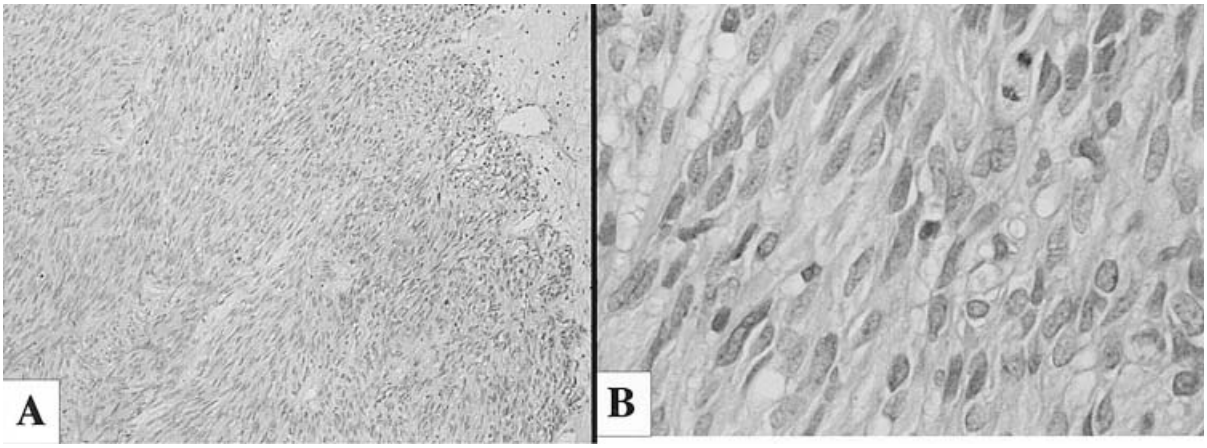


Fig. 5. The histological findings of the specimen by hematoxylin-eosin staining. Magnification is ×100 in Fig. 5A, and ×400 in Fig. 5B.

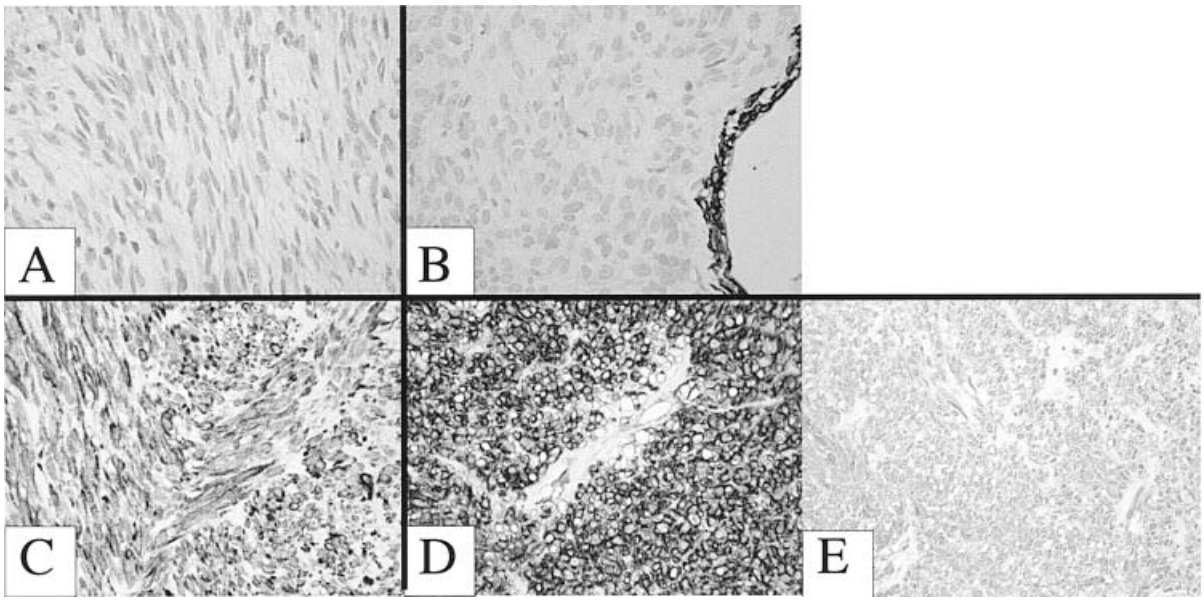


Fig. 6. The specimen findings of by the immunohistochemical staining. The original magnification is ×200 in each figure. The specimen was negative for S100 protein (Fig. 6A) and α-SMA (Fig. 6B), and, positive for vimentin (Fug. 6C), CD34 (Fig. 6D), and c-kit (Fig. 6E).

length, 10 cm ; e.d., 18 mm ; i.d., 16 mm ; Boston Scientific Co.) between the oral portion of the narrow segment in the upper body of the stomach and the anal portion (Fig. 7). After palliative treatment with SEMS, her dysphasia significantly improved, and she could eat solid food. The upper gastrointestinal series showed good passage of the contrast-medium through the implanted stent. On 23 February, 2001, she was discharged, and could eat regular food. She was readmitted to our hospital on 1 August, 2001, complaining of loss of appetite and general fatigue. An upper gastrointestinal series showed the narrowing of SEMS, and the CT findings showed prominent enlargement of the tumor, especially in the left upper abdominal cavity. A jejunostomy was performed for tube feeding on 13 August, 2001 and she was discharged on 22 September, 2001. She then stayed at home with tube feeding, and was examined regularly by a family doctor. Early in January, 2002, she became markedly emaciated, and died at home on 16 February, 2002.

## DISCUSSION

Gastrointestinal stromal tumors (GISTs) in the broad sense are commonly defined as primary mesenchymal tumors of the gastrointestine, arising from cells located in the walls of the organ (1). However, the pathologic evaluation of GISTs is dif-

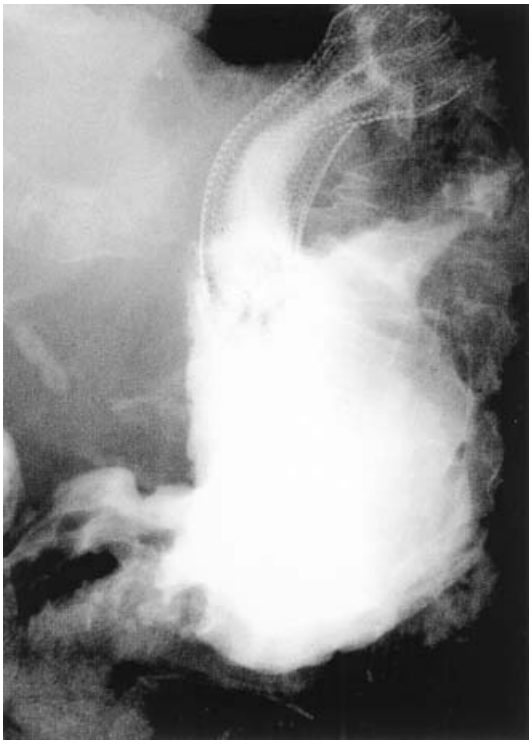

Fig. 7. Upper gastrointestinal series after implantation of the self-expandable metallic stent.

ficult and controversial (2). Most GISTs were traditionally classified as smooth muscle tumors (2). For the progression of the immunohistochemical examination, it was recently demonstrated that a large number of tumors, which had been described as GISTs, originated from gastrointestinal autonomic nerve cells (3). It was reported that several tumors were differentiated as neither the smooth muscle type nor the neural cell type, and GISTs of this uncommitted type were often demonstrated to reveal a positive reaction for CD34 (4), a myeloid progenitor cell antigen presenting in endothelial cells and some fibroblasts (4). From these findings, Rosai divided GISTs into four major categories on the basis of their phenotypical features : 1) Smooth muscle type : Tumors showing differentiation toward the smooth muscle cells, as evidenced immunohistochemically by the expression of smooth muscle actin and desmin and ultrastructually by the presence of pinocytonic vesicles, subplasmalemnal dense patches, and cytoplasmic microfilaments with focal densities; 2) Neural type : Tumors showing apparent differentiation toward the neural elements, mainly determined by the presence on ultrastructural examination of neuron-like features such as long cytoplasmic processes resembling axons joined by primitive cell junctions, scattered microtubules consistent with neurotubules, and dense-core neuro-secretary type granules. Immunohistochemical support for this interpretation has been meager, in the sense that neural/neuroendocrine markers such as neurofilaments, chromogranin, and synaptophysis have generally been absent and the only markers in this category showing consistently positive results have been the less reliable neuro-specific enolase and/or S-100 proteins ; 3) Combined smooth muscle-neural type : Tumors showing dual differentiation toward the smooth muscle and neural elements ; 4) Uncommitted type (GISTs in some restricted sense) : Tumors lacking differentiation toward either cell type, even after exhaustive immunohistochemical and ultrastructural probing. These tumors are often positive for CD34 (1).

Interstitial cells of Cajar (ICCs), which exist in the smooth muscle layer of the gastrointestinal tract, have recently been considered as the pacemakers of gastrointestinal autonomous mobility (5). In 1992, Maeda *et al*. reported that only in the indigenous gastrointestinal cells was the KIT receptor of the c-kit gene products were demonstrated on the surface of the cells, which were considered as ICCs (6). In 1998, Hirota *et al*. reported that KIT receptor was not found in typical smooth muscle tumors or neural tumors, however, it was positive in 94% of GISTs (7). Miettinen *et al*. previously described that GISTs were positive for CD34 (4). Hirota *et al*. described that GISTs might be derived from ICCs, because ICCs were double-positive for CD34 and the KIT receptor (7). Chan *et al*. proposed that a definite diagnosis of GISTs should be taken by the demonstration of the KIT receptor, which would be a c-kit gene product. On the basis of this finding, they classified gastrointestinal mesenchymal tumors as follows : 1) GISTs which are positive for c-kit, and many of them are also positive for CD34 ; 2) Smooth muscle tumors which are positive for desmin, but negative for c-kit ; 3) Neural tumors, are positive for S-100, but negative for c-kit ; 4) Others (5). The tumor in this case was positive for both c-kit and CD34, therefore, the definite diagnosis was GIST in Chan's classification. Furthermore, this tumor fulfilled the criteria of the uncommitted type in Rosai's classification.

There have been no definite criteria for the features of clinically benign and malignant tumors. The features purported to have prognostic importance include tumor size, mitotic count, cellularity, nuclear pleomorphism, cell type, and growth pattern (8). Several studies have reported that tumor size and mitotic counts are as important as the prognostic

factors (2, 8). In Ackerman's Surgical Pathology, GISTs were divided into three groups according to the tumor size and mitotic rate, as follows. 1) benign : mitotic count less than 5 mitotic figures per 50 high-power-field (HPF) ; 2) borderline : same mitotic number but a tumor size large than 5 cm ; 3) malignant : mitotic count greater than 5 mitotic figures per 50 HPF, any size tumor (1). However, several studies suggested that the only accurate evaluation for malignant tumors is in the evidence of circumferential invasion and distant metastasis (9, 10).

Few studies have been reported which described the features of image diagnosis for GISTs. Fujiwara *et al*. reported that angiography showed the abundant feeding vessels of the tumor and tumor staining, plain computed tomography (CT) featured basically the iso-density tumors that sometimes include low density areas, enhanced CT showed the increased density that might reflect the abundance of tumor vessels, and, T1-weighted MRI showed low intensity in contrast to high intensity in T2-weighted MRI (9).

With respect to the prognosis, Ueyama *et al*. reported that the 10-year survival rates of patients with gastric sarcoma or intestinal sarcoma were 74% and 17%, respectively, therefore, the sarcoma had a more favorable prognosis when it occurred in the stomach rather than in the intestine (2). However, Morita *et al*. recently reported that any GIST should be followed up as a potential malignant tumor in the long term, because neither definite criteria nor indicators for malignant tumors have been established (11). In this case, the intra-operative findings showed evident invasion to the circumferential tissues, such as the diaphragm, retro-peritoneum, and the lesser omentum, despite no evidence of distant metastasis. According to the findings in this case, the tumor was larger than the critical size of 5 cm and the mitotic rate was also very high. These findings suggest that the tumor should be defined as malignant. In addition to her advanced age, our patient had grave cardiac complications of atrial fibrillation, and therefore, we considered her to be unable to endure the aggressive surgical treatment of thoracotomy. The findings of the laparotomy revealed massive invasion and easy bleeding from the tumor. Therefore, we had to restrict the operative procedure, and only performed an incisional biopsy in consideration of the patient's perseverance against surgical damage.

The efficacy of various prostheses has recently been reported for palliative treatment against dysphasia due to non-curable esophageal or stomach malignancies (12-15). In comparison with conventional plastic protheses, many studies have reported that this SEMS has the advantage of easy deployment, and thus, a high placement success rate and a low-rate of complications, such as perforation, hemorrhage, and pain especially during the early phase post-placement (12-15). In addition, the great advantage of SEMS lies in the low level of discomfort for the patient during the stent implantation procedures (15). SEMS consists of various types, such as Wallstent, Z stent, and Ultraflex (14). However, it has not been concluded which prothesis is the best and safest. Complications were also related to design problems with these protheses (15). Ultraflex stents of the non-covered type was recently reported to be unable to generate sufficient radical force for expanding scirrhous and bulky neoplasmas (12). On the other hand, it was reported that the non-covered type metallic stents had a higher risk of migration of the neoplasma than the covered type of metallic stent (15). In this case, we obtained a definite diagnosis postoperatively as a malignant GIST. The preoperative image and the intra-operative findings showed that the tumor originated from the stomach wall and extended extraluminally. We expected a low possibility of tumor invasion into the stomach lumen, and we therefore used a non-covered Ultraflex stent for the ease of placement, and the low possibility of displacement, and we were already accustomed to implanting this stent.

Esophageal hiatus hernia is a common disorder in the upper gastro-intestinal organs, and is often found, especially in elderly women. Kawai *et al*. recently reported cases of the upside-down type of esophageal hiatus hernia, which were complicated with gastric cancer (16). They also suggested the difficulty of correctly diagnosing a malignant tumor when the stomach is herniated to the mediastinum in the esophageal hiatus hernia, because the precise diagnosis is distorted even though various image techniques are used (16). This case had the sliding type of hernia, but not the upside-down type. It is suggested that the early detection of GIST in the stomach is faciliated using images, such as an upper gastro-intestinal series and upper gastrointestinal endoscopy when the tumor extends into the gastric lumen. Furthermore, the tumor symptoms might appear during an earlier stage. In this case, the extra-luminal extension of the GIST may have delayed the appearance of the stenosis, thus delay-

ing the definite diagnosis.

In conclusion, we should consider the rare association of GIST when a patient is examined and the condition is clinically diagnosed as esophageal hiatus. For palliative treatment against non-resectable GIST, the implantation of a self-expandable metallic stent, Ultraflex, was useful to improve the patient's quality of life in this case.

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