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A Case of Gastrointestinal Stromal Tumor of the Stomach

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In a 55-year-old man, a tumor about 3 cm in diameter was detected in the upper abdomen by abdominal ultrasound screening during follow-up of chronic hepatitis C discovered in 1990. There were no symptoms and no abnormalities on physical examination. Tests for tumor markers were negative. By barium meal and gastroscopy, submucosal tumor was found on the lesser curvature of the stomach, with bridging fold in the absence of central ulceration. Biopsy revealed no tumor tissue. Under the diagnosis of submucosal tumor of the stomach, either a leiomyoma or leiomyosarcoma, partial resection of stomach was performed. Direct invasion of the surrounding organs, lymph node metastasis or distant metastasis was not observed grossly in the operation. Histologic examination of the resected specimen revealed proliferation of spindle cells and oval cells in an interlacing pattern. Immunohistochemistry for CD34, vimentin and c-kit protein was strongly positive, while smooth muscle actin, S-100 protein, desmin and p53 protein were negative. The proliferating cell nuclear antigen index was about 50%, while the MIB-1 index was ≤ 1%. From these findings, this tumor was diagnosed as a gastrointestinal stromal tumor of the uncommitted type.

Keywords : Submucosal tumor of the stomach, GIST, uncommitted type, Immunohistochemistry, CD34, c-kit protein

INTRODUCTION

Mesenchymal neoplasms of the gastrointestinal tract have hitherto been pathologically diagnosed as leiomyoma, leiomyosarcoma, or schwannoma based on light microscopy, whereas immunohistochemical and electron microscopic studies have disclosed the presence of tumors with unclear cellular differentiation. Recently, some investigators have proposed that such lesions should be called gastrointestinal stromal tumors (GISTs) [1, 2]. However, there is no uniform view on the preoperative diagnosis, treatment, and prognosis of GISTs. Since the number of reports on GISTs is still too small in Japan as compared with overseas, it is important to document cases of this tumor that are properly diagnosed histologically.

We experienced a patient with GIST detected by screening ultrasonography, which was immunohistochemically diagnosed as an uncommitted type of GIST. We report this case here with some discussion of the literature.

CASE REPORT

The patient was a 55 year-old man. A tumor about 3 cm in diameter was detected in the upper abdomen by abdominal ultrasound screening during follow-up of chronic hepatitis C discovered in 1990, and he was admitted for investigation and treatment on November 10th, 1998.

Past history: The patient had a gastric ulcer in 1985. Since 1998, he has been on oral therapy for hypertension and diabetes mellitus. Since 1990, he has been under observation for chronic hepatitis C.

Family history: Not contributory.

Findings on admission: The patient was 163 cm tall and weighed 60 kg, with a well-nourished physique. The blood pressure was 146/88 mmHg and the pulse rate was

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78/min (regular). No signs of anemia or jaundice were present. No abdominal mass or superficial lymph nodes were palpable. The skin was normal.

Laboratory tests on admission: There were no hematological or biochemical abnormalities. Tests for tumor markers (CEA, CA19-9, AFP) were negative.

Barium meal: On the lesser curvature of the stomach, a mass with a gently elevated margin and bridging folds was observed, indicating a diagnosis of submucosal tumor of the stomach. No central ulceration was noted (Fig. 1).

Fig. 1 Upper GI series shows a mass with a gently elevated margin on the lesser curvature of the stomach.

Gastroscopy: An ulcerated tumor covered with mucosa, suggestive of a submucosal tumor, was found on the lesser curvature of the stomach. Biopsy revealed no tumor tissue (Fig. 2).

Abdominal ultrasonography: A solid tumor measuring about 41 × 37 mm was found between the left lobe of the liver and the stomach; the surface was slightly irregular and a cystic component was evident (Fig. 3). The tumor moved with respiration similarly to the stomach, suggesting that it was a primary gastric tumor. There was no lymph node enlargement or findings suggesting hepatic metastasis.

Abdominal CT scanning: The CT findings were similar to those of ultrasonography. CT with contrast enhancement revealed that the tumor was relatively hypervascular and the left gastric artery and vein were dilated. However, there was neither lymph node enlargement nor hepatic metastasis (Fig. 4).

Gallium scintigraphy: There was no gallium accumulation in the tumor.

Since these results indicated a diagnosis of submucosal tumor of the stomach, either a leiomyoma or leiomyosarcoma, surgery was performed on November 13, 1998.

Operative findings: When the abdomen was opened via an upper midline incision, there was a soft primary gastric tumor the size of an infant's fist on the lesser curvature of the stomach. The vagus nerve was adherent to its surface and was not dissectable. The lesion was excised with a 2 cm margin of apparently normal gastric tissue using a Linear Stapler to divide the gastric wall. There was no enlargement of the surrounding lymph nodes suggestive of metastasis. Intraoperative histologic examination disclosed bundles of spindle cells, and the rapid pathologic diagnosis was gastrointestinal stromal tumor (GIST) with 4 mitotic figures per 50 hpf.

Pathological examination of the resected specimen: The tumor was a solid extragastric mass (35 × 35 mm) with cystic degeneration and internal bleeding. Microscopic examination revealed proliferation of spindle cells and oval cells arranged in interlacing pattern. The spindle cells had elongated nuclei with mild atypia and eosinophilic or clear cytoplasm (Fig. 5). The cellularity was intermediate and there were a few mitotic figures (4/50 hpf). No tumor necrosis was found. Immunohistochemistry for CD34 (Fig. 6), vimentin, and c-kit protein (Fig. 7) was strongly positive, while smooth muscle actin, S-100 protein, desmin, and p53 protein were negative. The proliferating cell nuclear antigen (PCNA) index was about

50%, while the MIB-1 index was 1%. From these results, the tumor was classified as a lesion of the uncommitted type.

DISCUSSION

GIST was classified into four types by Rosai *et al.* [1] and Erlandson *et al.* [2], and these tumors are included in the largest category of primary nonepithelial tumors of the gastrointestinal tract (Table 1).

The light microscopic, immunohistochemical, and electron microscopic features of each type of GIST are as follows.

1) The smooth muscle type includes leiomyoma and leiomyosarcoma, with light microscopy showing bundles of spindle cells. Tumors with pronounced cellular atypia and many mitotic figures are believed to be

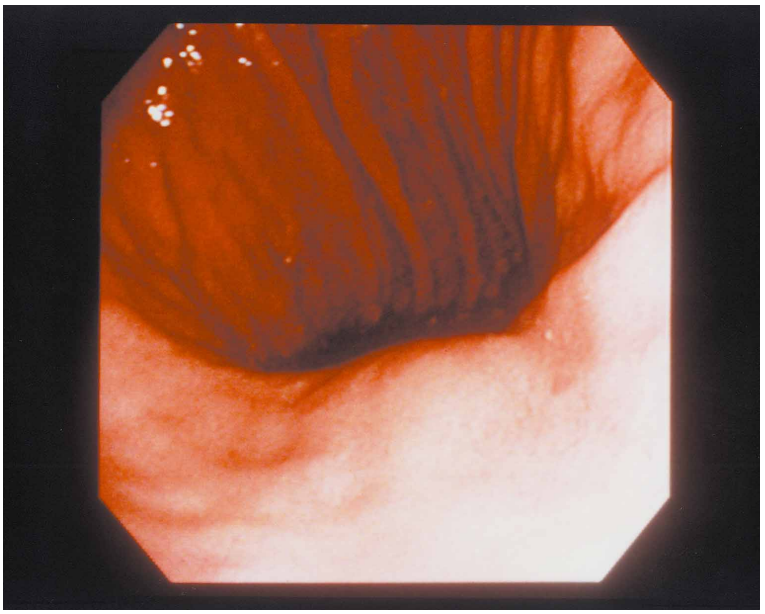

Fig. 2 Gastroscopic finding shows a tumor covered with mucosa on the lesser curvature of the stomach.

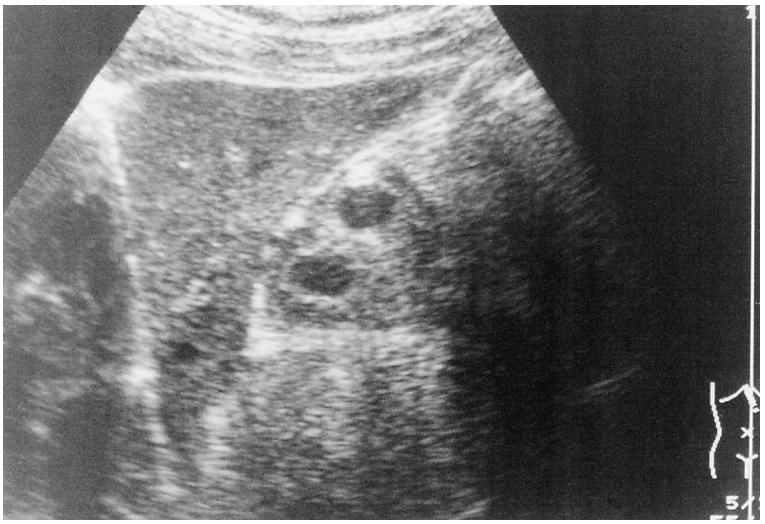

Fig. 3 Abdominal ultrasonography shows a solid tumor measuring about 41 × 33 mm between the left lobe of the liver and stomach.

Table 1 Four major categories of GIST according to the phenotypical features from Ackerman's Surgical Pathology.

1. smooth muscle type
2. neural type
3. combined smooth muscle-neural (mixed) type
4. uncommitted (undifferenciated) type

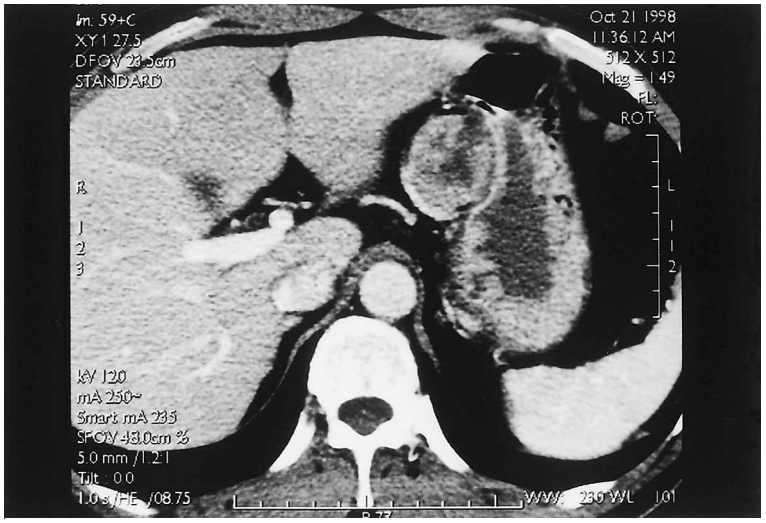

Fig. 4 Contrast-enhanced CT scan findings were similar to those of ultrasonography.

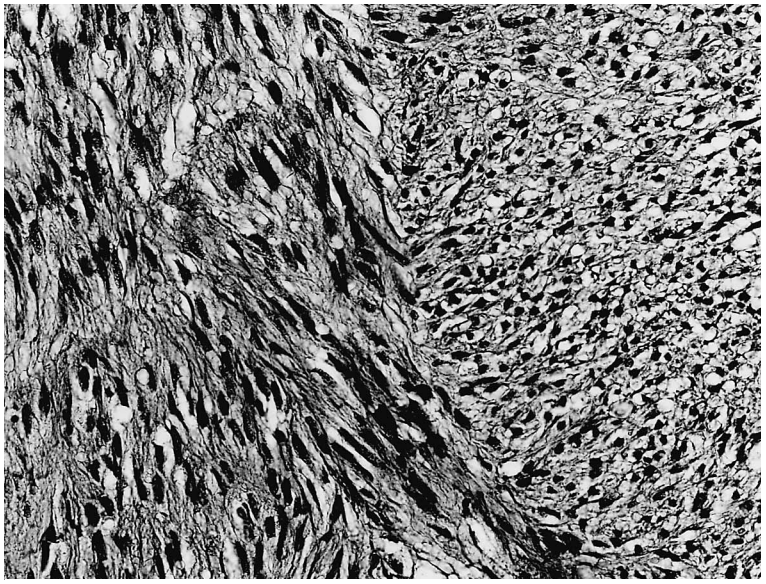

Fig. 5 Histologic section of the tumor. The spindle cells and oval cells arranged in an interlacing pattern. (× 300)

malignant. Immunohistochemical tests are positive for myogenic markers such as desmin and smooth muscle actin, and are negative for neurogenic markers including S-100 protein. On electron microscopy, the presence of pinocytotic vesicles as well as actin filaments forming dense bodies are characteristic. This is the most common type of GIST [1–3, 5].

2) The neural type is considered to be synonymous with gastrointestinal autonomic nerve tumor as proposed by Walker *et al.* [4]. Light microscopically, it is characterized by bundles of spindle cells as is type 1, and vacuoles may be seen within the cell bodies. Immunohistochemistry is usually negative for neurofilament, chromogranin, and synaptophysin, which are markers of neurons and neuroendocrine cells, and is negative for myogenic markers. Neuron-specific

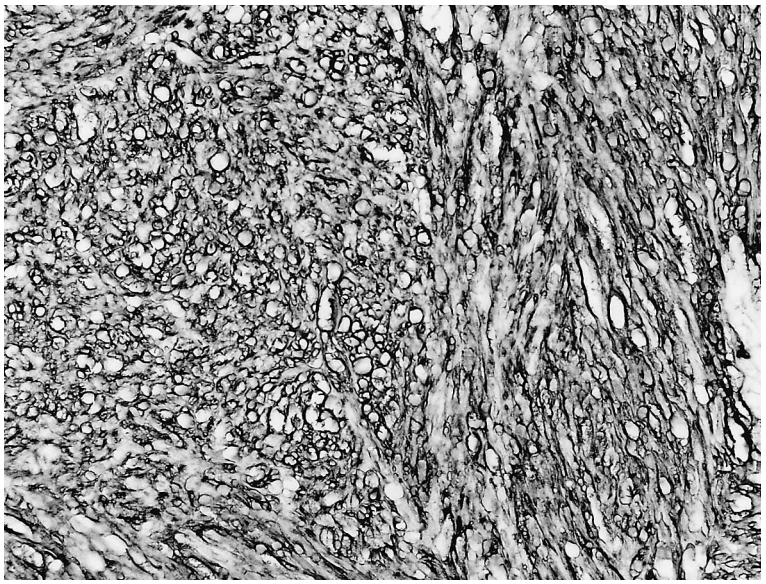

Fig. 6 Immunohistochemical studies show many of the tumor cells are CD34 positive.

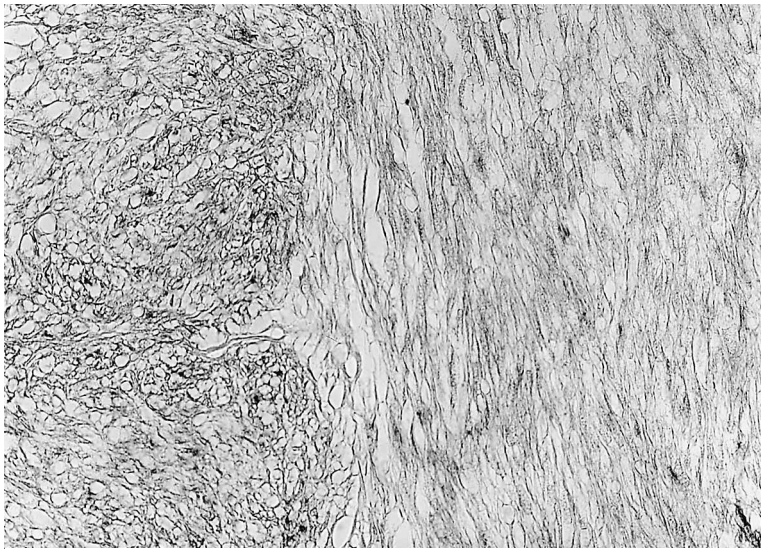

Fig. 7 Immunohistochemical studies show many of the tumor cells are c-kit protein positive.

enolase and/or S-100 protein are the only neurogenic markers that are positive [1, 2, 4].

Electron microscopy shows synapse-like structures in the cytoplasmic processes, and the absence of actin filaments is characteristic [4, 5].

3) The combined smooth muscle-neural (mixed) type of GIST can differentiate into either the smooth muscle type or the neural type, and is the least common. These tumors are usually considered to be malignant [1, 2].

4) The uncommitted (undifferentiated) type shows no clear differentiation into either the smooth muscle type or the neural type, and immunohistochemistry is often positive for vimentin and CD34 [1, 3, 6]. Positivity for CD34, which is also expressed by vascular endothelial cells and some fibroblasts, is particularly common. This type accounts for about 15% of all GISTs. These tumors are considered to be malignant or potentially malignant [1].

GISTs commonly occur in persons between 50 and 60 years of age, and less commonly in those aged 40 or younger, but most patients with malignant disease are in the younger age group. There is no sex difference in the incidence. The ratio of benign to malignant tumors is reported to be 10: 1. GISTs can develop in any part of the gastrointestinal tract, but the most common site is the stomach (50–70%) followed by the small intestine (25–30%), while the colon, rectum, and esophagus are rarely involved. Hemorrhage and upper abdominal pain are the common presenting symptoms of GIST of the stomach, with the incidence being 40–50% in benign tumors and about 85% in malignant ones. As tumor malignancy increases, the diameter also increases and the frequency of palpable tumors rises to 60–70% [9, 10]. In addition to the above-mentioned histologic features, expression of c-kit protein (CD117) was recently reported in type 4, which is generally considered to be GIST in a narrow sense [7, 8].

Whether the tumor was benign or malignant was not established in the present patient. According to Ackerman [1] and Miettinen [3], a definitive diagnosis is made on the basis of tumor diameter, the presence/absence of intratumoral necrosis, the presence/absence of hemorrhagic foci, cellularity, nuclear atypia, mitotic figures, direct invasion of surrounding structures, and distant metastasis. The invasion of surrounding structures, distant metastasis, tumor diameter, and mitotic figures are important; tumors with <5 mitotic figures per 50 hpf and a diameter ≤5.0 cm are considered to be benign, while those with ≥5 mitotic figures per 50 hpf are malignant. Tumors with a diameter >5.0 cm and <5 mitotic figures per 50 hpf are borderline [1, 9, 10]. The present patient had 4 mitotic figures per 50 hpf, the tumor diameter was 3.5 cm, intratumoral necrosis was absent, the cellularity was intermediate, and there was no direct invasion of surrounding structures or distant metastasis, but the PCNA index was 50% (≥10%), indicating that the tumor is potentially malignant. In our study of GISTs, gastric tumor site, tumor size, lack of necrosis, interlacing pattern, low mitotic count, low MIB-1 labeling, and not-so-high cellularity indicate non aggressive favorable prognostic character of tumor [12].

Although the treatment of GIST has not been established, lymph node metastasis is reportedly uncommon (≥10%) [10]. Thus, extended lymphadenectomy is not required and resection with at least a 2-cm clear surgical margin is usually sufficient [1, 9, 10]. Since the intraoperative histologic examination of the present patient showed a low number of mitotic figures (4/50 hpf) and the tumor diameter was only 3.5 cm, lymph nodes were sampled to confirm the absence of metastases and partial gastrectomy was performed.

Some physicians have administered adjuvant chemotherapy (adriamycin, doxorubicin, ifosfamid, etc.) and adjuvant radiotherapy to patients with malignant tumors that have a high likelihood of recurrence, but such treatment has little effect on the prognosis [9, 10].

Regarding the prognosis, the reported five-year survival rate varies widely from 20% to 70% even for malignant GIST, and the biological behavior of these tumor is still unknown [9–11].

Common sites of metastasis are liver (60–70%), lung (25%), and bone (25%). Distant metastasis has been reported more than five years postoperatively. Accordingly, the present patient needs to

remain under follow-up for a long period [9, 10].

With regard to GIST, nationwide standardization of the pathologic diagnosis by light microscopy, immunohistochemistry, and electron microscopy as well as preoperative imaging, improved accuracy of endoscopic diagnosis, and investigation of more patients all appear to be important for determining management policies and assessing the prognosis.

CONCLUSION

We reported a 55-year-old man with primary GIST of the stomach that was immunohistochemically classified as being of the uncommitted type.

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