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Gastrointestinal Stromal Tumor (GIST) Originating in the Rectum: Report of Two Cases

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Two cases of gastrointestinal stromal tumor (GIST) originating in the rectum are reported. The first patient was a 44-year-old man (Case 1) who underwent abdominoperineal resection (APR) for a diagnosis of smooth muscle sarcoma of the rectum. No adjuvant therapy was administered. Seven years 8 months after the operation, hepatic metastasis (S3 region of the liver) was diagnosed, and excision of the lateral segment of the liver was performed. The patient is alive 5 months after the operation. The second patient was a 43-year-old man (Case 2) with smooth muscle sarcoma of the rectum diagnosed by intraoperative frozen section examination, and APR was performed. Two years after the operation, local recurrence and multiple hepatic metastases were diagnosed. Two years later, metastasis to the lung was diagnosed. The patient was treated by microwave coagulation therapy under CT guidance for local recurrence and TAE for liver metastasis, and systemic chemotherapy, but died 5 years and 3 months after the operation. Immunohistchemical staining of the tumor specimens obtained from these patients revealed that the tumors were strongly c-kit- and CD34-positive, clear evidence for a diagnosis of GIST. Since there have been few reports in the literature of patients with recurrence or metastasis of definite GIST originating in the rectum, we report our two cases of rectal GIST.

Key words: rectal GIST, rectal smooth muscle sarcoma, hepatic metastasis

Introduction

We reviewed two cases of smooth muscle sarcoma of the rectum in which hepatic metastasis and local recurrence developed postoperatively. Until recently, non-epithelial tumors of the digestive tract were classified as leiomyoma, smooth muscle sarcoma, or schwannoma. However, the existence of gastrointestinal stromal tumor (GIST) in the strict sense, which does not exhibit clear differentiation into either nerve or muscle, has recently been recognized in immunohistological studies. The patients were definitively diagnosed by immunohistochemical analysis as having GIST arising in the rectum.

In this paper we report these cases encountered in Japan together with some discussion based on the literature.

Case Reports

Case 1

A 44-year-old man was admitted to the hospital because of thinning of stools. At 24 years of age he had been underwent the operation of appendicitis. The patient's parents and siblings had no history of remarkable diseases. The patient had a history of bleeding per rectum since around 1990. Although he consulted a local physician at that time, no specific diagnosis was made. A stool specimen was found to be positive for occult blood during a routine examination in 1992, but again no specific diagnostic procedure or treatment was considered. In 1993, during another health examination, the patient's stool specimen was again found to be positive for occult blood, whereupon the patient was examined and admitted to our department for further examination and treatment on suspection of a submucosal tumor of the rectum, approximately 6 cm in size.

Palpation during the rectal examination revealed a goose-egg-sized tumor with a smooth surface and hard elastic consistency in the 9 to 12 o'clock position. Palpation of the abdomen revealed a smooth enlarged liver and spleen that were soft in consistency. No superficial inguinal lymph nodes were palpable. Laboratory findings on admission, there was no anemia. Serum biochemical parameters, including the serum transaminase and electrolyte levels, were normal. The serum CEA level was 5.1 ng/ml, and was slightly above normal. Barium enema shows that a tortuous lesion with a smooth margin, approximately 6 cm long, was observed protruding from the anterior wall 2～3 cm above the dentate line (Fig. 1).

In colonoscopic findings, a tortuous lesion with a gentle slope was observed 3～4 cm above the dentate line, and suspected of being a submucosal tumor. Biopsy led to a diagnosis of leiomyosarcoma. A CT scan of the abdomen and pelvis obtained after the intravenous injection of contrast material revealed no evidence of hepatic metastasis or enlarged lymph nodes. MRI findings in the pelvis revealed that a lobulated tumor with a smooth margin, 6×5 cm in size, mainly occupying the anterior wall of the rectum was noted. The lesion was hyperintense and hypointense the T2- and T1-weighted images, respectively. A homogeneous high-contrast area was found, and no infiltration of the adjacent organs or structures in the pelvis was detected (Figs. 2a, b).

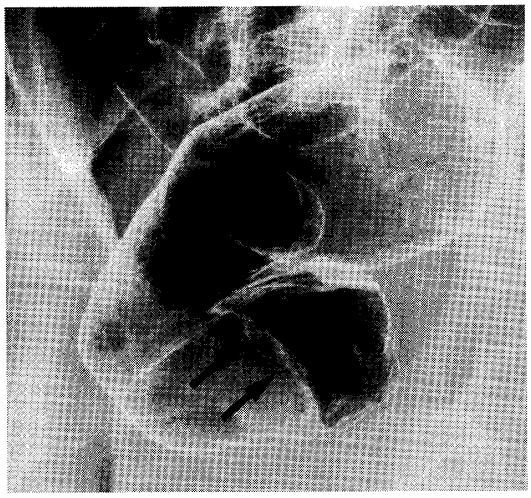

Fig. 1 Barium enema findings
A smooth protruding lesion, extending 6 cm, in the anterior wall 2～3 cm above the dentate line

Based on these findings, a diagnosis of smooth muscle sarcoma of the rectum was made, and abdominoperineal resection was performed. In macroscopic findings of the resected specimen, a tumor measuring 6×5×3.5 cm and having a relatively smooth surface, was observed protruding into the lumen from the wall of the rectum (Fig. 3a). Histopathologically the disorganized proliferative spindle cells with baculiform nuclei were observed. There were relatively few mitotic figures, and a diagnosis of well-differentiated leiomyosarcoma of low-grade malignancy was made (Fig. 3b). Since on immunohistochemical staining the tumor was strongly c-kit- and CD34-positive, and somewhat positive for α-smooth muscle anti-

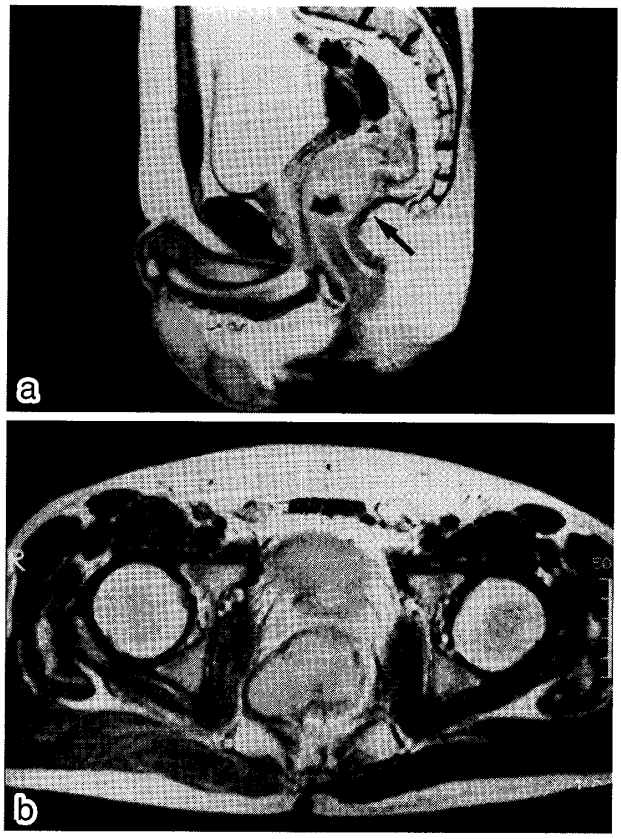

Fig. 2 MRI examination of the pelvis
(a) Sagittal profile (T2-weighted image): a tumor, 6× 5 cm in size, is seen in the anterior wall of the rectum. (b) Transverse section (T 2-weighted image): no marked infiltration of adjacent organs or structures is visible in the pelvis.

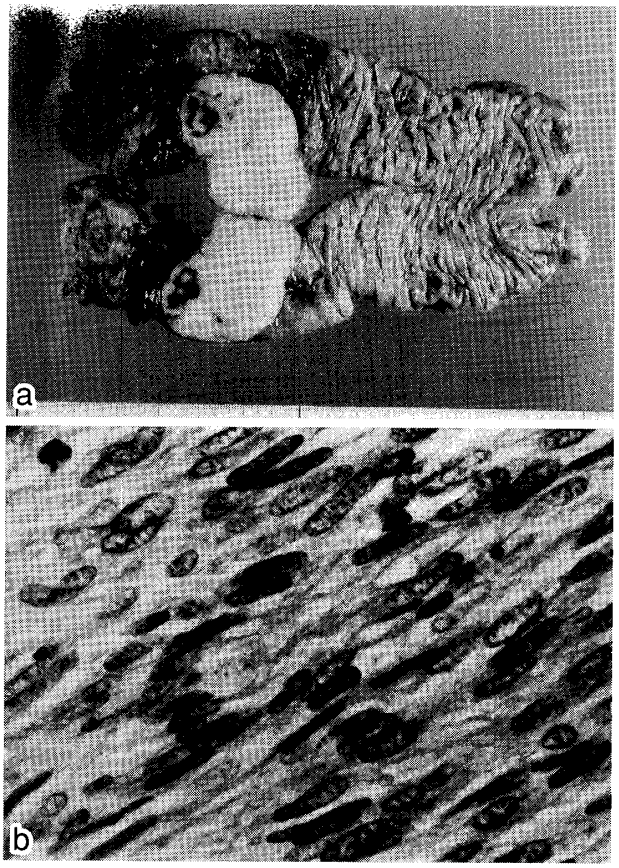

Fig. 3 Macroscopic examination of the resected specimens and histopathological findings
(a) Off-white tumor protruding from the lumen, (b) Disorganized proliferative spindle cells with comparatively few mitotic figures (HE staining, × 400).

gen (SMA), neuron specific enonase (NSE), vimentin, and S100, a definitive diagnosis of GIST was made.

The patient received no adjuvant therapy postoperatively, and recovery was uneventful. Eight years after the operation, however, a metastatic tumor, 7 cm in size, was observed in the S3 region of the liver (Fig. 4), the lateral segment of the liver was resected. Histopathological examination of the tumor specimens revealed cells similar in morphology to those observed in the primary tumor, and immunohistochemically c-kit- and CD34-positive, indicating that it was a metastatic sarcoma. The patient is alive without recurrence, 5 months after the hepatic resection.

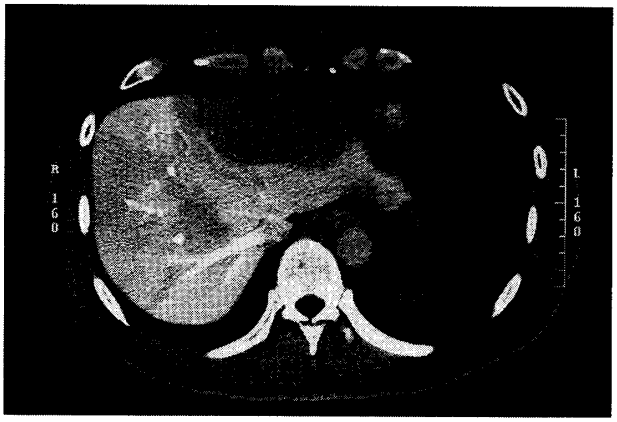

Fig. 4 Abdominal CT findings
A metastatic tumor, 7 cm in size, is seen in the S3 region in the liver.

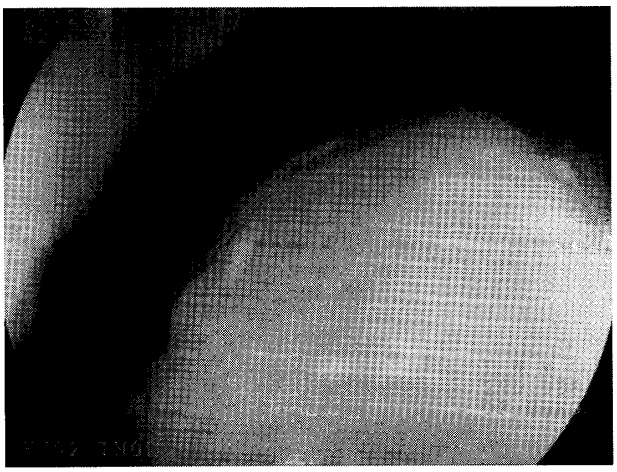

Fig. 5 Colonoscopic findings
A tortuous lesion with a gentle slope that touches the dentiform line and occupies one-fourth the circumference of the anterior wall of the rectum is seen.

Case 2

A 43-year-old man was admitted to the hospital because of the constipation and the pain in the hypogastric region on the left side. The patient had consulted a local physician for complaints of them since March 1996. A rectal tumor was diagnosed. The patient had had no history of gastrointestinal diseases. There was no family history of remarkable disease.

Palpation during the rectal examination revealed a chicken-egg-sized tumor with a smooth surface and hard elastic consistency extending about 4 cm from the anal margin in the 1 to 2 o' clock direction. No other abnormal findings were noted. Hematological, serum-biochemical, and urinary examinations revealed no abnormalities; serum levels of tumor markers were within normal limits. Barium enema showed a smooth protrusion in the anterior wall of the Rb region of the rectum. Colonoscopic findings revealed a tortuous lesion with a gentle slope that touched the dentiform line and occupyied one-fourth of the circumference of the anterior wall of the rectum was observed (Fig. 5). No confirmatory diagnosis could be obtained by biopsy.

A CT scan of the abdomen and pelvis obtained after the intravenous injection of contrast material, confirmed no hepatic metastase. A superficially lobulated tumor 5 cm in size with central necrosis was found arising from the anus and rectum. MRI examination of the pelvis showed a marginally prominent tumor about 4.5 cm in size arising from the left anterior and lateral wall of the rectum. It was observed as hypointense on the T1-weighted images and as a combination of both hypo-intense and slightly hyperintense on the T2-weighted images.

Based on these findings, per anal local resection was performed. Since intraoperative frozen section examination yielded a diagnosis of smooth muscle sarcoma, an abdominoperineal resection was performed. Lymph nodes in the lateral regions were not removed. Vagotomy was not performed. In macroscopic examination of the resected specimen, the specimen was off-white in color and turgid, and it measured 4 × 3 cm; no infiltration of the mucosa was observed. The tumor was lobulate and encapsulated, and central bleeding was noted.

Histopathologically, disorganized hyperplastic spindle cells enclosed by a fibrous capsule were observed, and a diagnosis of leiomyosarcoma of low-grade malignancy was made. The histological examination showed bleeding, degeneration, and calcification. No infiltration of the rectal mucosa or vascular invasion was observed. Since immunohistochemical analysis revealed that the tumor was strongly positive for c-kit and CD34 (Fig. 6), and somewhat positive for SMA, NSE, and vimentin, a definitive diagnosis of GIST was made.

Multiple hepatic metastases (Fig. 7a) and local recurrence (Fig. 7b) were diagnosed 2 years 1 month after the operation. TAE was performed out 6 times for hepatic metastases, and microwave coagulation therapy under CT guidance

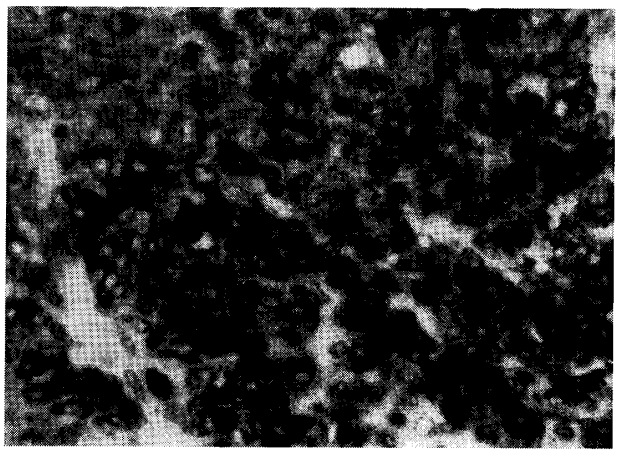

Fig. 6 Immunohistochemical analysis (c-kit staining, ×400): strongly positive.

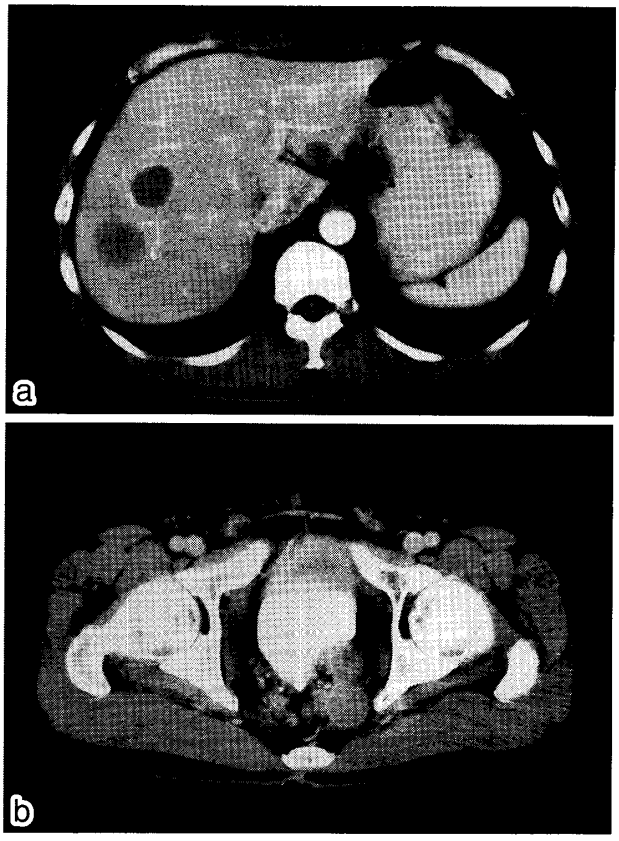

Fig. 7 Abdominal and pelvic CT findings
(a) Multiple hepatic metastatic tumors are seen.
(b) Local recurrence is visible in the left lateral rectal region and the anterior aspect of the sacrum.

was administered for local recurrence, but neither was adequately satisfactory. Four years after the operation, pulmonary metastasis was discovered, but despite the institution of chemotherapy (DTIC: 140 mg×3 day, CPA: 400 mg×1 day, DXR: 50 mg×1 day, VCR: 1 mg×1 day) and TAE twice for the hepatic metastases, the patient died 5 years 3 months after the operation, of hepatic insufficiency resulting from progressive disease.

Discussion

GIST in the broad sense is a general term for mesenchymoma arising from the digestive tract. Based on differences in tendency toward differentiation, Rosai[1] classified GIST into 4 types: a smooth muscle type, exhibiting differentiation to muscle; a neural type, exhibiting differentiation to neural tissue; a combined smooth muscle-neural type, exhibiting differentiation to both muscle and neural tissue; and an uncommitted type, exhibiting differentiation to neither muscle nor neural tissue. Of these four types, the uncommitted type is regarded as GIST in the strict sense. Recent immunohistochemical studies have revealed c-kit to be a specific marker of GIST[2)~8)], however since GIST is an only recently established concept, few cases have been reported.

We screened the Igaku Chuo Zasshi (Japana Centra Revuo Medicina)[2)~6)] for cases of GIST arising from the rectum reported in Japan as the end of 2001, and found 16 cases, and the cases in the present report brought the total to 18 cases (Table). Most of the patients has been in their fifties or sixties. The cases have comprised 10 males and 8 females, and there has been no clear sex predilection. The presenting symptoms diverse and included melena, anal pain, hypogastric pain, constipation, and anal tumor. Barium enema and colonoscopy revealed a protrusion from the wall of the rectum in every case.

Vascular proliferation with dense tumor staining on scintigraphic examination has been reported, although we did not perform this examination. Tumor biopsy and immunohistochemical study (c-kit, CD34) are essential to making a de-

Table Cases of gastrointestinal stromal tumors originating from the rectum in Japan

No.	Author	Year	Age	Sex	Chief complaint	Outcome	c-kit	CD34
1	Ito[2]	1997	67	F	anal bleeding	5 M alive		+
2	Takahashi[2]	1999	57	F	abd. fullness	7 M alive	+	+
3	Takahashi[2]	1999	33	F		120 M alive	+	+
4	Takahashi[2]	1999	51	F		108 M alive	+	+
5	Takahashi[2]	1999	47	M		24 M dead	+	+
6	Takahashi[2]	1999	44	M		72 M alive	+	+
7	Ito[2]	1999	89	F	anl bleeding	alive	+	+
8	Yokoi[2]	1999	67	F		36 M alive		+
9	Matsumoto[19]	2000	57	M	anal pain	alive	+	+
10	Imazu[20]	2000	70	M	abd. pain	alive	+	+
11	Ikehata[2]	2000	65	F	anal pain	42 M alive		+
12	Sawada[2]	2000	62	M	buttock tumor	alive	+	+
13	Taihei[21]	2000	51	M	anal pain	72 M rec., 5 M alive		+
14	Hirahara[5]	2000	71	M	anal incongruity	12 M alive	+	+
15	Ogata[3]	2001	55	F	mass in vagina	10 M alive	+	+
16	Nozawa[6]	2001	80	M	anal bleeding	8 M alive	+	+
17	Bamba	2001	44	M	thinning of stools	96 M liver meta., 5 M alive	+	+
18	Bamba	2001	43	M	constipation	25 M local rec. and liver meta., 63 M alive	+	+

M: month

finitive diagnosis of GIST. In some of the cases reported, surgery had been performed before confirmation of the diagnosis. Since chemotherapy and radiotherapy are often in effective, surgical resection of GIST is the treatment of first choice. Abdominoperineal resection has been the most common surgical procedure for rectal GIST.

Local recurrence and metastasis developed in six cases reported in the literature[7] and in both cases reported in this paper. In 4 of the cases recurrence was diagnosed more than 6 years after the operation[7], and in two of them the recurrence was detecteded 10 years after the operation[7], probably because of the low degree of malignancy and slow growth of the tumor. Recurrence is usually in the form of local recurrence, hepatic metastasis, or lung metastasis; however, most of the cases reviewed had only local recurrence[7,9]. TAE has been reported to be effective in the treatment of liver metastasis arising from GIST of the digestive tract[7,10,11].

Before the concept of GIST had become well established, slight positivity for SMA and S-100 was considered the basis for the diagnosis. Thus, it is conceivable that some cases of GIST in Japan have been included in the statistical analysis of cases of smooth muscle sarcoma. However, there are still few reports of cases of GIST, and the number is insufficient for comparison with smooth muscle sarcoma. GIST and rectal cancer have several features in common: ① poor sensitivity to chemotherapy and radiotherapy[12], ② stage of malignancy not necessarily reflecting the outcome[7], ③ removal of lymph nodes being unnecessary in most cases[3], ④ long-term follow-up for over 10 years being necessary[9], ⑤ the prognosis being comparatively good[13,14].

The prognosis of patients of GIST with transmutation of exon 11[8] of the c-kit gene is not as good as that of patients with no such transmutation [9,15,16]. It has been reported[17,18] that selective c-kit tyrosine kinase inhibitors may be effective in the treatment of patients with multiple hepatic metastases and peritoneal recurrence, in whom

resection is not feasible. STI571 in this class has recently been approved by the US Federal Drug Administration (FDA)[18].

It may be necessary to review all cases of smooth muscle sarcoma diagnosed in the past in order to survey patients with rectal GIST (uncommitted type) and follow their clinical progression. Novel therapies using novel drugs can be expected in the near future.

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直腸原発 GIST（gastrointestinal stromal tumor）の2例

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直腸原発 gastrointestinal stromal tumor（GIST）の2例を経験したので報告する．症例1は44歳男性である．直腸平滑筋肉腫の診断で，腹会陰式直腸切断術（APR）を施行した．補助療法は行わず，術後7年8カ月目にS3肝転移を認め，肝外側区域切除を行い，現在生存中である．症例2は43歳男性である．術中迅速病理診断で直腸平滑筋肉腫の確定診断を得たため，APRを行った．術後2年目に局所再発および多発肝転移を来し，術後4年目には肺転移を認めた．CT下マイクロウェーブ凝固療法，化学療法，TAEで加療を行ったが，術後5年3カ月目に死亡した．両症例に後日免疫組織化学染色を施行し，c-kitおよびCD34が強陽性を示していたことから狭義のGISTと診断された．直腸原発GISTの症例の報告は少ない．本邦における直腸GISTの報告例とともに，若干の文献的考察を加え報告する．