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Single Case

Multiple Small Bowel Gastrointestinal Stromal Tumors Associated with Neurofibromatosis Type 1 that Were Not Detected by Endoscopy: A Case Report

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Keywords
Gastrointestinal stromal tumors · Neurofibromatosis · Neurofibrome type 1 · Small bowel tumor · Balloon-assisted enteroscopy

Abstract
We treated a 39-year-old Japanese man who was admitted for an abdominal mass. He had had neurofibroma-like skin lesions since childhood. Computed tomography and endoscopic ultrasound results were consistent with a tumor in the small intestine. Although the tumor was undetectable by single-balloon endoscopy, the patient's background and imaging results led us to suspect a gastrointestinal stromal tumor (GIST). He also met the diagnostic criteria for neurofibroma type 1 (NF1). We performed a surgical removal of the tumor, and the biopsy results led to a definitive diagnosis of GIST. Small bowel GISTs should be considered in cases of NF1.

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Introduction

Neurofibroma type 1 (NF1) is an autosomal dominant disorder that presents with characteristics of skin lesions (neurofibromas, café au lait spots) that is reported to affect 1 in 2,600–3,000 people [1, 2]. An individual harboring multiple such skin lesions should be further examined to determine whether they meet the diagnostic criteria for NF1. The National Institute of Health (NIH) diagnostic criteria for NF1 state that at least two of the following criteria must be met for a clinical diagnosis: six or more café au lait macules over 5 mm in prepubertal individuals and over 15 mm in postpubertal; two or more neurofibromas (one if plexiform); freckling in the axillary or inguinal regions; two or more Lisch nodules; distinctive osseous lesion such as sphenoid dysplasia or thinning of long bone cortex; first-degree relative with NF1.

Gastrointestinal manifestations are seen in 15–20% of all NF1 patients, and almost all reported cases are gastrointestinal stromal tumors (GISTs). GISTs associated with NF1 are most frequently located in the small intestine and present with multiple lesions, whereas non-NF1-related GISTs usually present as a single lesion predominantly in the stomach. In addition, 65% of NF1-associated GISTs are asymptomatic. Unlike most other GISTs, NF1-associated GISTs are usually KIT/PDGFR-α negative [2, 3]. The standard treatment for NF1-associated GISTs is surgical removal sometimes followed by imatinib treatment.

We treated a patient with asymptomatic NF1-associated GISTs that presented with multiple lesions within the small intestine. Although a biopsy revealed KIT positivity, the genetic testing result confirmed c-kit mutation negativity. The CARE Checklist has been completed by the authors for this case report, attached as online supplementary material (for all online suppl. material, see www.karger.com/doi/10.1159/000529340).

Case Report

A 39-year-old Japanese man was admitted to our hospital for further examination of an abdominal mass that had been observed at a medical checkup 2 months prior. He had had neurofibroma-like skin lesions on his upper and lower extremities since his early childhood, but he had never sought medical aid for the lesions as he had no other subjective symptoms. There were no axillary frecklings or bone dysplasias. Ophthalmic examination revealed no Lisch nodule or optic nerve glioma. His father had similar skin lesions, but they were very few and had never been examined. Abdominal ultrasound performed at the abovementioned checkup revealed an abdominal mass located behind the bladder measuring 55 mm in diameter.

There were no significant laboratory data findings on admission to our hospital (Table 1). Upon physical examination, multiple neurofibroma-like skin lesions were seen on his extremities and back (online suppl. Fig. 1a). Several café au lait macules were seen on his upper extremities. The patient thus met the NIH diagnostic criteria for NF1: having ≥6 café au lait macules, ≥2 cutaneous neurofibromas, and a first-degree relative with a possible case of NF1. The pathological findings from the patient's skin biopsy performed later at our hospital were also consistent with NF1.

Abdominal computed tomography (CT) scans revealed a mass within the pelvic cavity measuring 63 × 41 mm in size attached to the small intestine on the cranial side (online suppl. Fig. 2a). The small intestinal branch of the superior mesenteric artery and vein flowed into the mass (online suppl. Fig. 2b). Multiple subcutaneous nodules were detected. Positron emission tomography-CT showed the maximum standardized uptake value of 4.70 accumulated in the intra-pelvic cavity tumor and the maximum standardized uptake value of 1.33 accumulated in

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Table 1. Patient's laboratory data on admission (39-year-old male)

Hematology			ALP	138	U/L
WBC	4,840	/μL	BUN	18.9	mg/dL
Neutrophils	75.0	%	Cr	0.84	mg/dL
Lymphocytes	15.3	%	Na	140	mEqL
Monocytes	7.2	%	K	4.6	mEq/L
Eosinophils	1.9	%	Cl	105	mEq/L
RBC	5.16	$\times 10^6$/μL	CRP	0.06	mg/dL
Hb	15.3	g/dL	ALP	138	U/L
Ht	45.3	%	BUN	18.9	mg/dL
PLT	15.1	$\times 10^4$/μL	Cr	0.84	mg/dL
Biochemistry			Serology		
ALB	4.6	g/dL	Adrenaline	30	pg/mL
T-BIL	1.9	mg/dL	Noradrenaline	289	pg/mL
AST	14	U/L	Dopamine	7.0	pg/mL
ALT	11	U/L	Insulin	3.7	μIU/mL

Laboratory data on admission to our hospital did not show any significant results.

ALB, albumin; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; Cl, chloride; Cr, creatinine; CRP, C-reactive protein; Hb, hemoglobin; Ht, hematocrit; K, potassium; Na, sodium; PLT, platelet; RBC, red blood cells; T-BIL, total bilirubin; WBC, white blood cells.

the subcutaneous nodules (online suppl. Fig. 2c). A small bowel series showed no significant findings (Fig. 1a).

Retrograde single-balloon-assisted enteroscopy (BAE) was performed. However, there was no irregularity of the bowel wall (Fig. 1b), and we performed ink-jet marking at the end-point. Despite there being a distinguishable mass within the pelvic cavity on the CT scan, there were no notable findings by the small bowel series or endoscopy. Endoscopic ultrasound (EUS) was performed in order to pinpoint the tumor location. We detected a tumor with blood flow and low echoic lesions within it on the medial side of the bladder (Fig. 1c). The tumor was not attached to the small intestine, colon, or bladder, and there was no apparent tumor invasion.

These findings led us to suspect small bowel GISTs associated with NF1. As GISTs do not require a preoperative definitive diagnosis and biopsies are associated with risks of dissemination, we did not perform a tumor biopsy via EUS. Other possible differential diagnoses were schwannomas and neurosarcomas.

We performed a laparoscopic partial small bowel resection for removal of the tumor and for an open biopsy. A fist-sized dark red tumor measuring 7.0 × 4.0 × 6.5 cm was found on the caudal side of the endoscopic marking on the pelvic diaphragm with phyllodes growth outside the small intestine (Fig. 2a). There was no adhesion to surrounding organs. On the cranial side of this tumor, multiple grain-sized (approx. 2.5 mm) extramural nodules were found (Fig. 2b). No notable nodules were observed on the liver surface. As these nodules were limited to the small bowel area, we suspected that these were also GISTs and not peritoneal dissemination.

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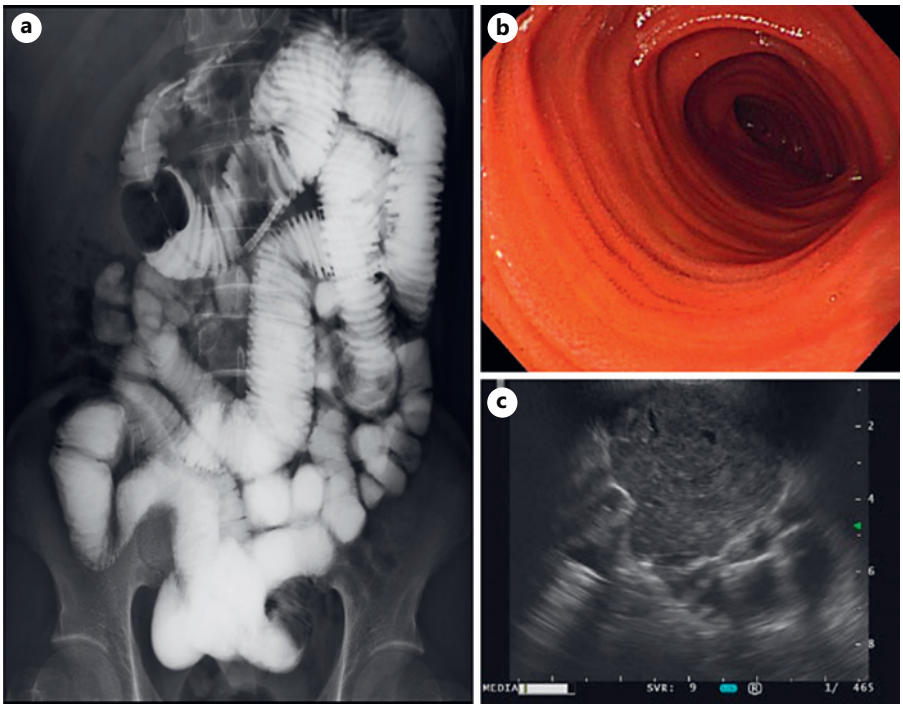

Fig. 1. Other imaging results. **a** A small bowel series showed no significant findings. **b** Retrograde balloon-assisted enteroscopy (BAE) showed no irregularity of the bowel wall. The tumor itself was undetectable via endoscopy. **c** On EUS, we detected a tumor with blood flow and low echoic lesions within it on the medial side of the bladder. The tumor was not attached to the small intestine, colon, or bladder, and there was no apparent tumor invasion.

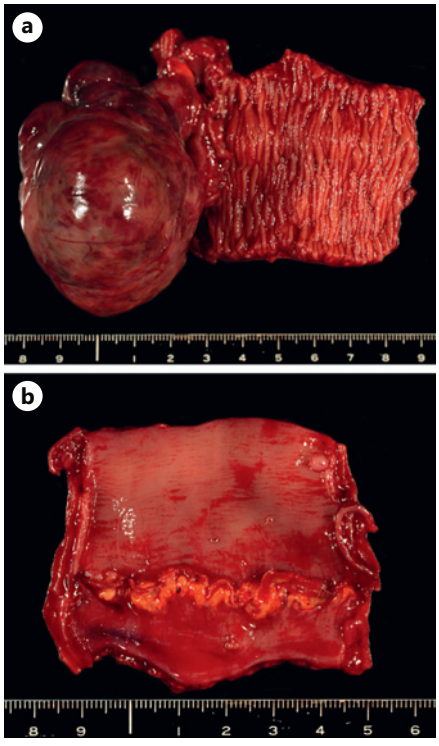

Fig. 2. a A fist-sized dark red tumor measuring 7.0 × 4.0 × 6.5 cm was identified on the caudal side of the endoscopic marking on the pelvic diaphragm with phyllodes growth outside the small intestine. **b** On the cranial side of this tumor, multiple grain-sized (approx. 2.5 mm) extramural nodules were observed.

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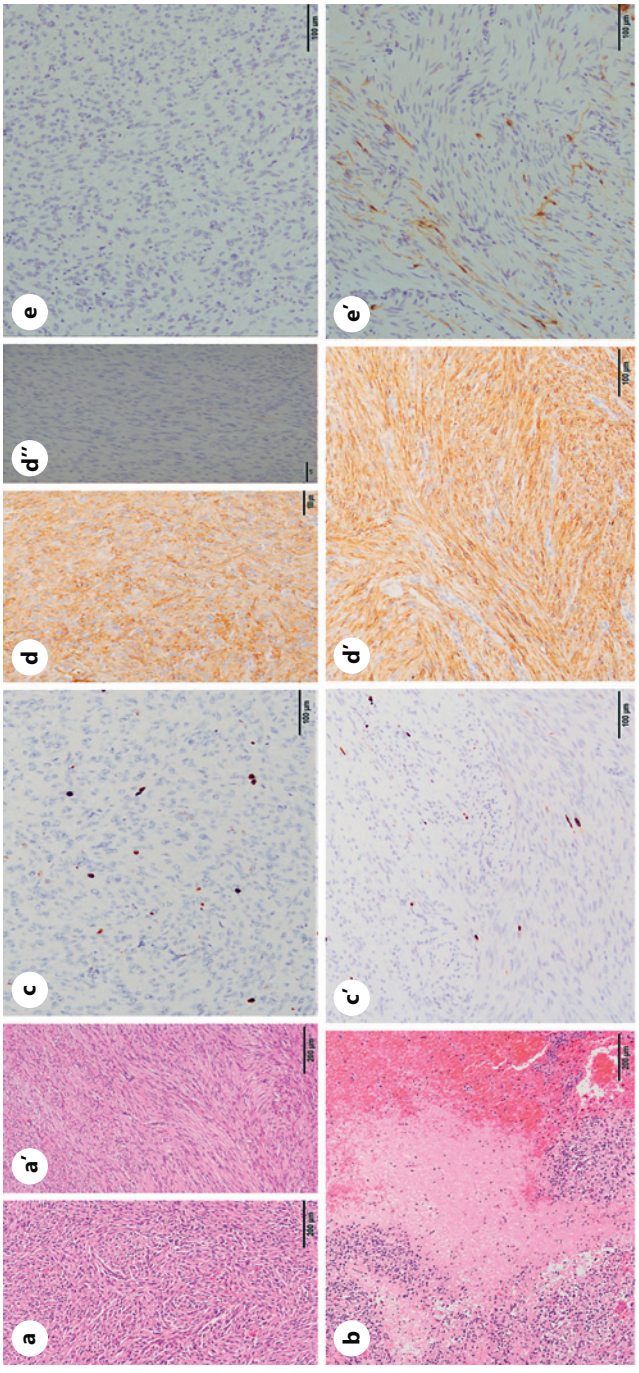

Fig. 3. Microscopic findings of the tumor. **a** Spindle-shaped cells arranged in bundles. **a'** Hematoxylin-eosin stain of the nodules. **b** Large areas of hemorrhage and necrosis. **c** Cell protein Ki-67 analysis of the tumor. **c'** Ki-67 analysis of the nodule. **d** The tumor was c-KIT positive. **d'** The nodule was also c-KIT positive. **d''** Negative control of c-KIT staining. **e** S-100 analysis of the tumor. **e'** S-100 analysis of the nodules.

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Table 2. Features of NF1-associated GISTs reported in the past

	Age	Gender	Ethnicity	Tumor size, mm	Tumor localization	KIT stain	c-kit (genetic testing)
Case 1	27	Female	Saudi Arabian	170 × 130	Small bowel	Positive	Negative
Case 2	63	Female	Japanese	32 × 48	Small bowel	Positive	Unknown
Case 3	65	Male	Japanese	35 × 20, 7 × 5	Small bowel	Positive	Negative
Case 4	54	Female	Hispanic	42 × 36	Duodenum	Positive	Unknown
Case 5	59	Female	Hispanic	60 × 40	Small bowel	Positive	Unknown
Present case	39	Male	Japanese	70 × 65, 2 × 2	Small bowel	Positive	Negative

Microscopically, the tumor consisted of spindle-shaped cells arranged in bundles (Fig. 3a). Large areas of hemorrhage and necrosis were identified (Fig. 3b). Immunohistochemical analysis revealed that the Ki-67 index was 5% (Fig. 3c, c'). Both the tumor and the surrounding nodules were positive for c-KIT (Fig. 3d, d'). We thus concluded that the tumor and surrounding nodules were multiple GISTs. The mitotic index was <5%, and according to the modified Fletcher classification [1], the tumor was a high-risk GIST. Postoperative adjuvant therapy was thus considered.

However, it is important to note that the patient's genetic testing results were confirmed to be c-kit mutation negative; the patient is therefore not currently undergoing imatinib treatment. No new lesions have been detected on follow-up imaging tests within the 16-month postsurgery period.

Discussion

We have provided the details of a case of multiple small bowel GISTs associated with NF1. GISTs are mesenchymal tumors of the gastrointestinal tract that originate from primitive cells known as the interstitial cells of Cajal [1]. Surgical removal of the patient's main lesion was performed, and follow-up CT scans have been performed every 6 months in the outpatient clinic. No new nodules have been detected on the imaging results to date.

BAE and small bowel capsule endoscopy are increasingly being used in the investigation of small bowel tumors. BAE is performed by oral or transanal insertion of the endoscope. Although it is possible to examine the entire small intestine in one endoscopic trial at times, in many cases, two or more endoscopic trials are required to examine the entire small intestine. Therefore, depending on the localization of the tumor, it may not be possible to reach the site of the tumor with a single insertion of a balloon small bowel endoscope [4, 5]. All of the previously reported cases of NF1-associated GISTs were detectable via endoscopy. In the present case, however, the GIST could not be identified by the transanal balloon small bowel endoscopy performed for localization, as the tumor had formed on the exterior of the intestine wall, making this case unique. This inability to detect the tumor upon endoscopy made other imaging examinations (CT, EUS), along with the knowledge that NF1 can present with small bowel GISTs, crucial for the diagnosis of suppository GISTs prior to surgical resection.

The surgical findings showed that the patient's GIST was located more lateral to the anus than the markings that were made at the single-balloon endoscopy end-point. It is important to note that some GISTs may not be recognized by endoscopy due to their growth pattern. Our finding of endoscopically undetectable NF1-related GISTs emphasizes the importance of

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keeping in mind that NF1 patients can harbor GISTs when arranging follow-up examinations. As 65% of NF1-related GISTs are asymptomatic, they are mostly diagnosed sporadically, as was the case with this patient.

Neurofibromin (the gene product of NF1) is located on chromosome 17, and it is an anti-oncogene that negatively regulates RAS pathway activity. Tumors in NF1 develop by dysfunction of this tumor suppressor. In contrast, non-NF1-related GISTs develop as a result of overexpression of the KIT receptor tyrosine kinase protein. This difference in genetic background is thought to be a major contributing factor to how NF1-related GISTs are c-kit negative on genetic testing, unlike most other typical GISTs [6, 7]. This may also be the reason behind the low incidence of high-risk GISTs in NF1. Table 2 provides the clinical and pathological features of our patient and those of five other reported NF1-associated GISTs [1, 2, 6, 8].

Imatinib is considered a standard treatment for postsurgical residual GISTs. However, as c-kit overexpression is absent in most NF1-related GISTs, the efficacy of tyrosine kinase inhibitors such as imatinib for treating residual tumors is unclear [8–10].

In conclusion, we have reported a case of multiple small bowel GISTs associated with NF1. Although a rare manifestation, the possibility of the presence of GISTs should be taken into consideration when examining a patient with a known history of NF1.

Statement of Ethics

The patient's treatment was conducted in accord with the Declaration of Helsinki and the ethical principles of Tokyo Women's Medical University Hospital. Written informed consent was obtained from the patient for publication of this article and all related images. All treatment concerning this case report and the publication of this case has been approved by the Tokyo Women's Medical University Ethics Committee on June 01, 2023. The committee requires no approval number for case reports.

Conflict of Interest Statement

The authors have no conflict of interest to declare.

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Author Contributions

Main author: Satomi Saito. Authors in charge of substantial contribution: Shun Murasugi, Maria Yonezawa, Yukiko Takayama, Takeshi Ohki, Hiromi Onizuka, Yoji Nagashima, and Masakazu Yamamoto. Authors in charge of revision: Teppei Omori. Authors in charge of final approval: Teppei Omori and Katsutoshi Tokushige.

Data Availability Statement

All data generated or analyzed during this study are included in this article and its online supplementary materials. Further inquiries can be directed to the corresponding author.

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