Late recurrence of low-risk gastrointestinal stromal tumor of jejunum diagnosed 30 years after tumor resection: A case report and literature review

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Abstract. Gastrointestinal stromal tumors (GISTs) have a significant risk of metastasis, although the degree varies in each case. The present report describes a case of late recurrence of GIST that was diagnosed 30 years after the primary tumor resection. An 80-year-old man was transported to Sanjo General Hospital (Sanjo, Japan) with hemorrhagic shock from gastrointestinal bleeding. Abdominal contrast-enhanced computed tomography revealed an 11.7-cm heterogenous tumor in the retroperitoneum adjacent to the third portion of the duodenum. The patient had a medical history of resection of 'leiomyoma' of the upper jejunum when he was 50 years old. Pathological examination using archival pathological samples revealed that the previously excised tumor was GIST because the tumor cells showed positive immunoreactivity for KIT and DOG1. Treatment was started with imatinib, a selective KIT tyrosine inhibitor, even though endoscopy failed to provide biopsy specimens. Positron emission tomography conducted on the 28th treatment day revealed that imatinib completely shut down ^{18}F-fluorodeoxyglucose uptake in the tumor, confirming that the tumor was imatinib-sensitive. A literature review yielded 12 GIST cases wherein metastases were diagnosed >10 years after primary tumor resection. Of the 12, four were originally diagnosed as benign. Clinicians should keep in mind that GISTs were formerly confused with non-GIST tumors and that there is a risk of relapse 10 years or later after curative surgery.

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Abbreviations: CT, computed tomography; FDG, fluorodeoxyglucose; FFPE, formalin-fixed and paraffin-embedded; GI, gastrointestinal; GIST, gastrointestinal stromal tumor; HPF, high-power field; PET, positron emission tomography

Key words: GIST, imatinib, immunohistochemistry, KIT, late recurrence, leiomyoma, PET, potentially malignant

Introduction

Gastrointestinal tumors (GISTs) are the most common mesenchymal tumors in the gastrointestinal (GI) tract. The tumors arise from the interstitial cells of Cajal and are genetically characterized by activating mutations in the c-*kit* or *platelet-derived growth factor receptor* (*PDGFR*) *alpha* gene (1,2). GISTs are considered 'potentially malignant' tumors that pose a significant risk of metastasis, although the extent of malignancy is dependent on tumor size, mitotic index, and tumor site (3). This concept implies that there is no such thing as an absolutely benign GIST even though the tumor is devoid of morphological features that would suggest a malignant nature from a classical pathological perspective. Prior to the establishment of the molecular biological and pathological concepts of GISTs in the early 2000s, GISTs could not be clearly discriminated from other mesenchymal tumors including leiomyoma, leiomyosarcoma, and neurogenic tumors owing to the similarity in morphology (4).

We herein report a case of an 80-year-old man with recurrent GIST. The primary tumor was diagnosed as a leiomyoma arising from the jejunum 30 years ago, and hence patient follow-up was discontinued. Although the patient did not know that the tumor excised 30 years ago was malignant, immunohistochemical analysis of archival pathological samples disclosed that the tumor was a low-risk GIST. Literature review indicates that the disease-free interval of this case is the second longest among the reported cases of GIST recurrence. Our report offers evidence supporting the concept of 'potentially malignant' GISTs and will help advance our understanding of the management of GIST patients.

Case report

The patient was an 80-year-old man who suddenly fainted and was transported to our hospital. Hemorrhage from the GI tract was suspected because the patient presented with melena associated with a state of shock. Gastroduodenal endoscopy performed immediately uncovered a large mass in the duodenum. The tumor showed a plateau-like appearance and was widely covered with normal mucosa. The tumor also formed shallow ulcers that were identified as the source of bleeding (Fig. 1). Hemostasis was realized by endoscopic cautery, and hemodynamics was stabilized after blood transfusion. Abdominal contrast-enhanced computed tomography (CT) revealed that the tumor was 11.7x8.7 cm in size and located in the retroperitoneum adjacent to the third portion of the duodenum. The tumor exhibited as an irregularly shaped mass with heterogenous enhancement and was encompassed by the abdominal aorta and the superior mesenteric artery (Fig. 2). Although these radiological findings strongly suggested that the mass was a metastatic tumor, the patient denied any history of cancer diagnosis or treatment. Furthermore, endoscopy and CT scans immediately conducted identified no possible primary malignancy. Biopsied specimens obtained by endoscopy provided no specific information owing to inappropriate sampling. Fine-needle aspiration biopsy was abandoned because of the significant risk of bleeding.

An in-depth interview revealed a history of surgery: the patient had undergone resection of a 'leiomyoma' of the jejunum 30 years ago. The surgical records documented that the tumor was located in the upper jejunum adjacent to the ligament of Treitz (4 cm distal) and excised *en bloc* with a short jejunal segment. Although the tumor showed exophytic growth, serosal status was not mentioned in the pathological report. That event was published as a case report because of a unique manifestation of GI bleeding (5). This history raised the possibility that the tumor excised 30 years ago might be a GIST and the current tumor was a locoregional recurrence of the jejunal tumor. We obtained archival pathological samples of that tumor and reanalyzed them with current standard pathology including immunohistochemistry for KIT and DOG1. KIT is a standard cellular marker for GISTs, and DOG1 is a currently identified marker for GISTs, which is more highly diagnostic than KIT. Specific antibodies were purchased from MBL, Tokyo (no. 566, dilution, 1:400) for KIT and Nichirei, Tokyo (no. 718041, dilution, 1:1) for DOG1. The tumor showed diffuse, strong immunoreactivity for both KIT and DOG1 (Fig. 3). Ki-67 labeling index was lower than 5%. On the basis of these findings, the previously excised jejunal tumor was diagnosed as a low-risk GIST [tumor size, 3.5 cm; mitotic index, 4/50 high-power fields (HPF)]. Using the formalin-fixed and paraffin-embedded (FFPE) tissues, we performed the polymerase chain reaction for c-*kit* gene analysis but were unable to obtain sufficient amplicons for sequencing owing to the low-DNA quality.

The patient consented to undergoing molecularly targeted therapy with imatinib mesylate after careful explanation of the high possibility of metastatic GIST. Imatinib therapy was started with the dosage of 400 mg daily once a day. Positron emission tomography (PET)/CT conducted on the 28th treatment day revealed that imatinib therapy completely shut down

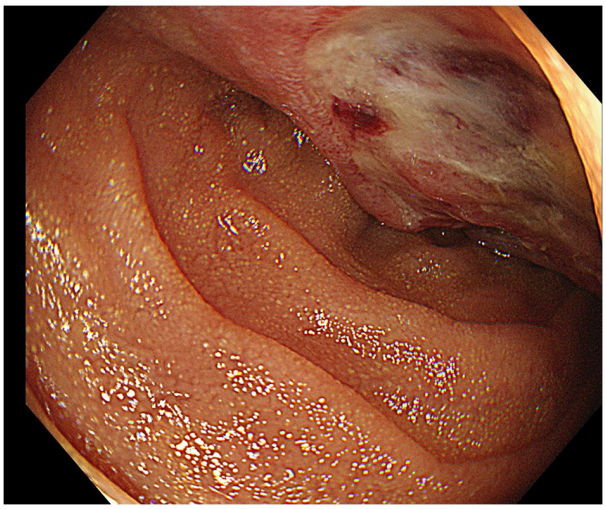

Figure 1. Endoscopic findings. Gastroduodenal endoscopy revealed a large plateau-like mass in the duodenum. The tumor was widely covered with normal mucosa and formed shallow ulcers.

^{18}F-fluorodeoxyglucose (FDG) uptake in the tumor (Fig. 4), confirming that the tumor was imatinib-sensitive.

Despite a short interruption due to an adverse event (grade-3 eruption), the patient continued imatinib therapy for 24 months and has shown partial response so far (Fig. 5).

Literature review

To characterize late-recurrence of GISTs, we searched the literature using PubMed database, designating 'gastrointestinal stromal tumor/GIST' and 'late recurrence/metastasis' as key words. The search gave twenty reports in English; careful examination revealed that one case series (6) and four case reports (7-10) met our research purpose. In addition, we reviewed the references of those reports and found further six case reports (11-16). Finally, we found a total of 12 cases of GIST recurrence that was diagnosed more than 10 years after the primary resection. A summary of their clinicopathological characteristics is presented in Table I.

Discussion

We present herein a case of a patient who suffered from recurrence of jejunal GIST 30 years after the primary tumor resection. We started imatinib therapy despite the lack of histological evidence by endoscopic biopsy because we were able to comprehensively make the diagnosis of locoregional recurrence of GIST on the basis of atypical imaging presentation on endoscopy and CT in addition to the patient's medical history of surgery for GIST of the upper jejunum. The diagnosis of GIST was finally confirmed by ^{18}F-FDG-PET, which showed that imatinib therapy definitely shut down ^{18}F-FDG uptake in the tumor. On the other hand, we could not obtain direct evidence that the tumor in the present case was a recurrence of the previously excised GIST and not a second primary one. Matching genotypes between the surgically excised tumor and the current one would offer strong evidence of 'recurrence'. Unfortunately, c-*kit* gene analysis was unsuccessful owing

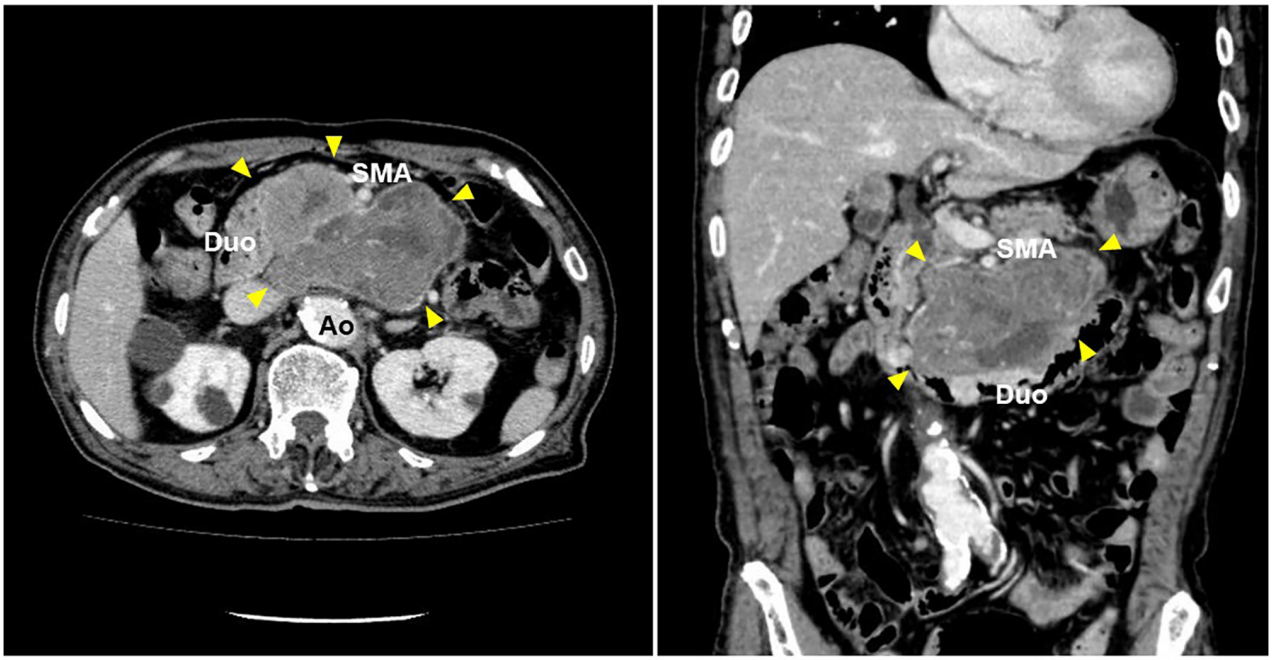

Figure 2. Abdominal contrast-enhanced computed tomography. Left, an axial slice; right, a coronal slice. The tumor was 11.7x8.7 cm in size and exhibited as an irregularly shaped mass with heterogenous enhancement (arrowheads). The tumor was encompassed by the Ao and the SMA and located in the retroperitoneum adjacent to the third portion of the Duo. Ao, abdominal aorta; Duo, duodenum; SMA, superior mesenteric artery.

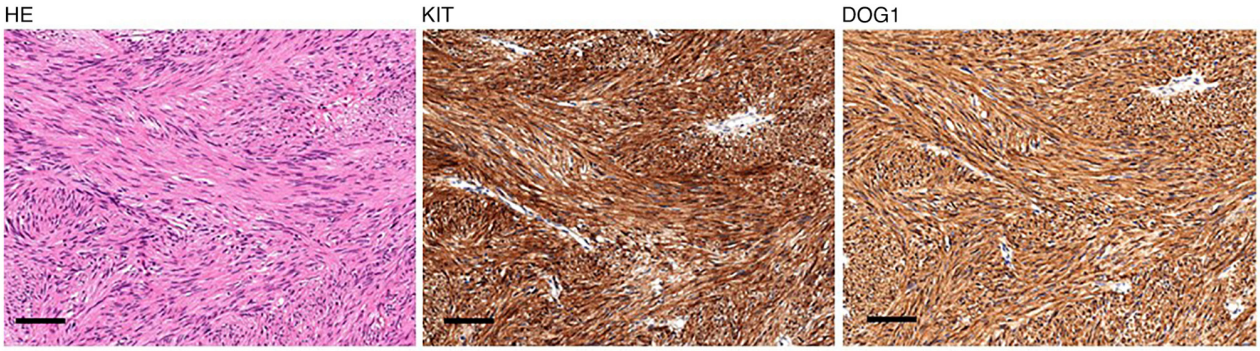

Figure 3. Pathological findings of the jejunal tumor surgically excised 30 years ago. The tumor predominantly comprised spindle cells that had a uniform cytology and showed a similar morphology to leiomyoma in HE staining. Immunohistochemical analysis revealed that the tumor showed diffuse and strong immunoreactivity for both KIT and DOG1 (original magnification, x200). Scale bars, 100 μm.

to low DNA quality. The diagnosis-treatment process in the present case was extraordinary and did not meet current clinical standards. However, the patient was at risk of re-bleeding and there was an urgent need to start treatment swiftly. This diagnosis-treatment process together with ^{18}F-FDG-PET may be warranted in suspected cases of GIST, particularly in an oncologic emergency.

GISTs are considered 'potentially malignant' tumors (17). Although it sounds ambiguous, this concept indicates that all GISTs have a significant risk of metastasis and none can be definitely labeled as benign. The primary tumor in the present case had been histologically diagnosed as leiomyoma, a benign myogenic tumor, on the basis of spindle-cell morphology. Utilizing current diagnostic standards including immunohistochemistry for KIT and DOG1, we re-evaluated archival FFPE samples and found that the tumor was a GIST. In 1990, the year the diagnosis was made, molecular understanding of GIST had been not established yet (1). Moreover, CD117 (KIT), a determinative immunohistochemical marker for GIST, was unavailable (18). The primary tumor in the present case was categorized as low malignant potential even by re-evaluation: mitotic index was 4/50 HPF and Ki-67 labeling index was lower than 5%. Our literature review also revealed that in four of 12 cases, the primary tumors were originally diagnosed as benign ones (Table I). These findings suggest that a clear-cut distinction between benign and malignant is impossible in the pathology of GISTs and support the current understanding that all GISTs should be dealt with as having a significant risk of recurrence.

The present case raises one clinical question: how long we should follow patients with low-risk GIST after potentially curable surgery (R0 resection)? The latest clinical practice guidelines of Europe (19) recommend a long follow-up of 10 to 13 years for high-risk GIST patients. Meanwhile, they propose a five-year follow-up for low-risk GIST patients after

Table I. Summary of cases of late recurrence of GIST diagnosed more than 10 years after primary tumor resection.

Author, year	DFI, years	Age at metastasis, years	Sex	Primary tumor	Site of metastasis	Diagnosis of primary tumor	Size of primary tumor, cm	Mitotic count, /50 HPF	Risk of primary tumor, modified Fletcher classification	Genotype	(Refs.)
Nannini *et al*, 2012	11	76	Female	Small bowel	Liver	n.m.	7	<1/30 HPF	n.m.	*KIT* exon 11	(6)
	11	70	Male	Rectum	Liver	n.m.	4	16	High	*KIT* exon 11	
Ballarini *et al*, 1998	11	62	Male	Stomach	Liver	Benign leiomyoblastoma	4	1	Low	n.m.	(7)
Furukawa *et al*, 2012	11	71	Male	Stomach	Port-site	Leiomyosarcoma	4	1	Low	*PDGFRA*	(8)
Whang *et al*, 2017	11	45	Female	Small bowel	Liver	GIST	11	n.m.	High	*KIT* exon 11	(11)
Masuoka *et al*, 2003	12	58	Male	Rectum	Liver	Low-grade leiomyosarcoma	4	2/10 HPF	High	n.m.	(12)
Nowain *et al*, 2005	17	56	Female	Small bowel	Liver	Leiomyosarcoma	10	n.m.	High	n.m.	(13)
Matsuoka *et al*, 2007	17	55	Female	Retroperitoneum	Liver	Leiomyosarcoma	14	n.m.	High	n.m.	(14)
Cahill *et al*, 2009	20	59	Female	Small bowel	Liver	Benign leiomyosarcoma[a]	6	5	High	n.m.	(15)
Grossi *et al*, 2019	23	79	Male	Stomach	Liver	Benign leiomyoblastoma	n.m	>10	High	*PDGFRA*	(16)
Ginori *et al*, 2015	29	71	Male	Duodenum	Liver	Schwannoma	2.5	1	Low	*KIT* exon 11	(9)
Ishizaki *et al*, 2020	32	72	Female	Small bowel	Liver	Leiomyosarcoma	n.m	<1	Low	n.m.	(10)
Current case	30	80	Male	Jejunum	Locoregional	Leiomyoma	3.5	4	Low	n.a.	

DFI, disease-free interval; GIST, gastrointestinal stromal tumor; HPF, high power fields; n,a, not analyzable; n.m., not mentioned; PDGFRA, platelet-derived growth factor receptor α. [a]Based on their report.

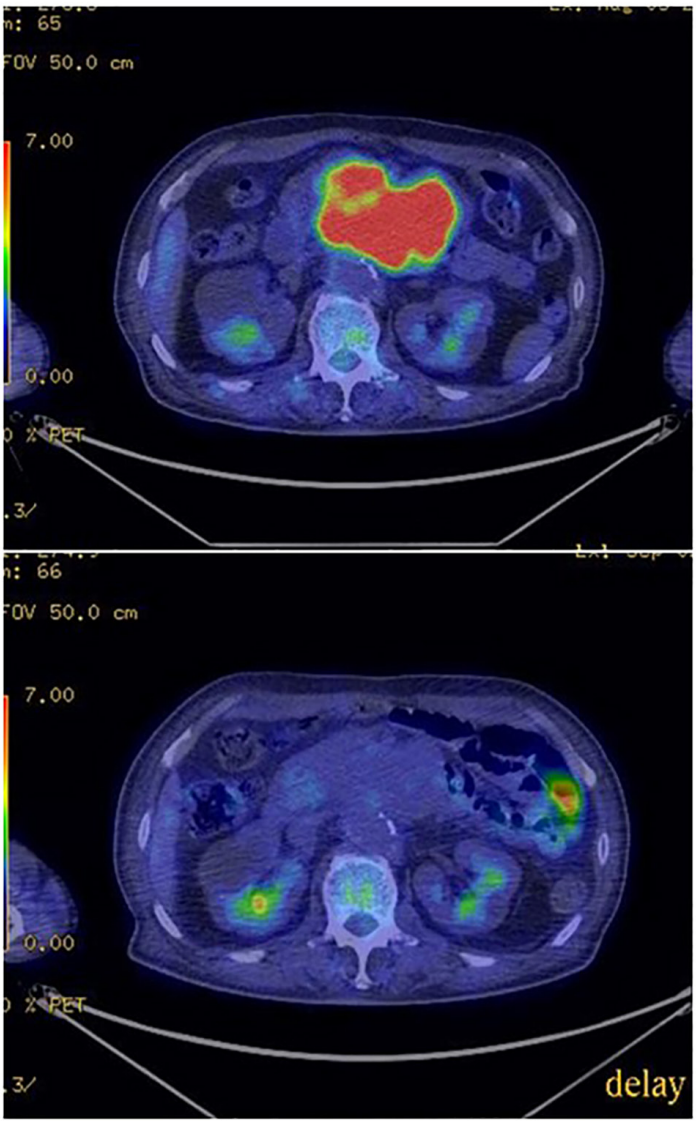

Figure 4. PET/CT images. PET/CT conducted immediately before imatinib therapy showed high ^{18}F-FDG metabolic activity (top), whereas that on the 28th treatment day revealed complete shutdown of ^{18}F-FDG uptake in the tumor (bottom). CT, computed tomography; FDG, fluorodeoxyglucose; PET, positron emission tomography.

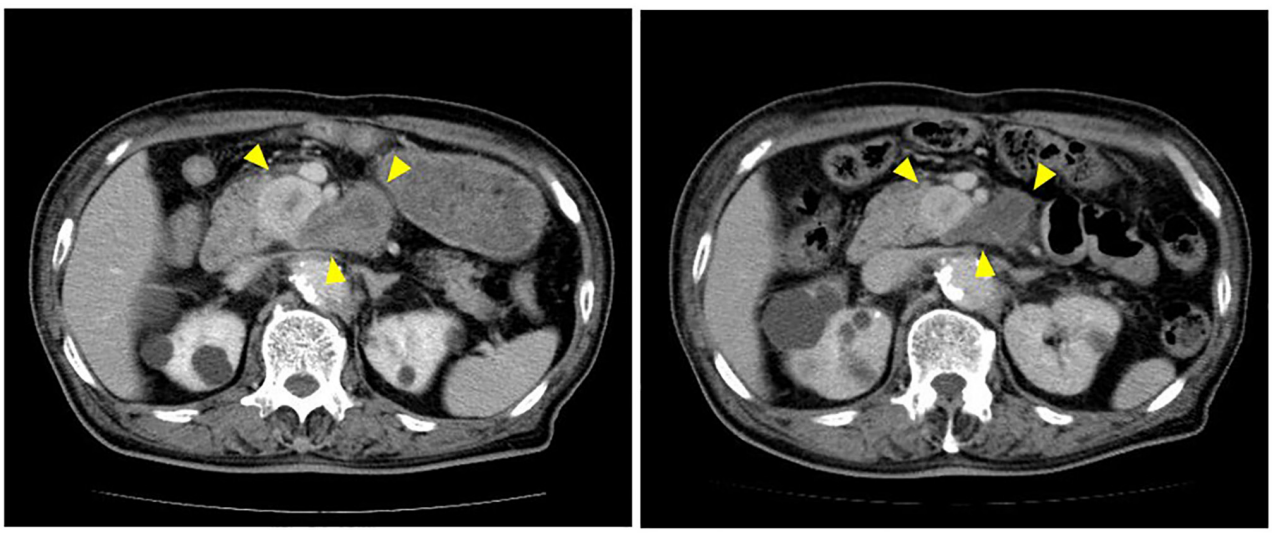

Figure 5. Tumor response. Contrast-enhanced computed tomography revealed that the tumor shrank to 7.3 cm in diameter 3 months after treatment (left) and showed maintenance of partial response after 24 months of treatment (right). Arrowheads indicate the tumor.

acknowledging lack of evidence on the clinical usefulness of that management.

Early retrospective studies on GIST recurrence (20,21) have revealed that the disease-free interval between primary tumor resection and diagnosis of recurrence is approximately two years in median and not largely different from that of common GI malignancies overall. On the contrary, two retrospective studies focusing on the late recurrence of GISTs have disclosed that considerable numbers of metastases occurred even after five years. In one study conducted by Italian researchers (6), reviews of 42 patients who underwent treatment for GIST recurrence in their institution indicated that the incidence of patients with late recurrence of five years or later was 14%. One Japanese study of 115 patients who developed recurrence after surgery (22) revealed that the incidence of late recurrence was 12.2%. These findings suggest that five-year follow-up is insufficient to determine the oncological outcomes of GIST patients, and longer follow-up is required. On the other hand, it was reported that the recurrence-free survival of low-risk GIST patients is 95% or higher (23), and the risk of late recurrence is extremely low in overall cases of low-risk GISTs. In addition, a study of the cost-effectiveness of follow-up of GIST patients showed that low-risk GIST patients needed 98 CT examinations and that it cost 15,484 euros to find one recurrence, which is approximately 7.5 times higher than that of high-risk GIST patients (24). Follow-up of selected patients would be the best solution. However, there is no known clinicopathological feature that can enable the effective selection of patients requiring long follow-up of more than five years. Although the above-mentioned Japanese study (22) revealed that small and low-risk GISTs were frequently found in cases of late GIST recurrence, those features are substantially useless for patient selection.

In conclusion, we have presented a case of late recurrence of jejunal GIST. The patient's history of surgical resection of 'leiomyoma' 30 years ago was a valuable hint that led to the diagnosis of recurrent GIST. Literature review of the late recurrence of GISTs indicated that a considerable number of tumors were previously diagnosed as benign mesenchymal tumors or low-risk GISTs. The present case, although anecdotal, offers supporting evidence that all GISTs have a significant risk of metastasis and therefore require longer follow-up than other malignancies. Clinical and surgical oncologists should keep in mind that disease relapse occurring 10 years or later after curative surgery for GISTs is possible.

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Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Authors' contributions

TK conceptualized the study and drafted the manuscript. TN and AW contributed to acquisition of data and prepared the images used in the manuscript. YI provided valuable information leading to a precise diagnosis and contributed to interpretation of data. SH conducted gene analysis of the archival samples. YA conducted immunohistochemical analysis and was responsible for pathological diagnosis. TK, TN, and YI confirm the authenticity of all the raw data. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Written informed consent was obtained from the patient for the publication of the case report and all accompanying images.

Competing interests

The authors declare that they have no competing interests.

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