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CASE REPORT

Gastrointestinal stromal tumors of the small intestine in pediatric populations: a case report and literature review

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Abstract An 18-year-old girl presented with abdominal pain and a tumor was subsequently detected in the jejunum. We therefore carried out a wedge resection of the jejunum. The diagnosis of GIST was confirmed histologically, and a mutation in exon 9 of the c-kit gene was observed. GISTs are rare in pediatric populations and pediatric GISTs occur predominantly in females and are characterized by a multifocal gastric location and a wild-type phenotype for the c-kit genes. The features of pediatric GISTs of the small intestine have not yet been categorized, and to date, only 11 cases in patients younger than 18 years have been reported. These cases did not occur primarily in females and tended to present as single tumors with mutations in the c-kit gene. This suggests that these cases do not have the same features as pediatric gastric GISTs, but instead are similar to adult GISTs. In pediatric populations, GISTs of the small intestine were expected to show a better response to imatinib treatment than gastric GISTs because of the alterations in the c-kit gene.

Keywords Gastrointestinal stromal tumor · Small intestine · Pediatric populations · The c-kit gene mutation

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Abbreviations

GIST	Gastrointestinal stromal tumor
CT	Computed tomography
PDGFRA	Platelet-derived growth factor receptor alpha
FDG/PET	18F-Fluorodeoxy-glucose positron emission tomography
SUV-max	Maximum standard uptake value
HPF	High-power fields

Introduction

Gastrointestinal stromal tumors (GISTs) are defined as mesenchymal tumors that arise from the gastrointestinal tract and occur predominantly in adults. These tumors typically show overexpression of the c-kit protein and have mutations in the c-kit or platelet-derived growth factor receptor alpha (PDGFRA) genes [1]. GISTs are usually observed in patients over the age of 40 and are extremely rare in pediatric populations.

Pediatric GISTs occur usually in female patients and manifest as multiple nodules in the stomach [2], with pediatric GISTs arising from the small intestine being extremely rare. Previous reports on GISTs in pediatric patients primarily described multiple gastric tumors and, to date, only 11 cases of GISTs of the small intestine in patients aged 18 years or younger have been reported in the English literature [3–12]. As a consequence, the clinicopathological features of pediatric GISTs of the small intestine have not yet been fully elucidated.

In this paper, we report the case of an 18-year-old female with a GIST of the small intestine and review 11 other reported cases in the literature. The purpose of this

article is to clarify the clinicopathological, immunohistochemical, and genetic features of GISTs of the small intestine in pediatric populations.

Case report

An 18-year-old girl presented with abdominal pain. The abdominal pain was not severe, but it was persistent. Therefore, we conducted an abdominal ultrasonography and subsequently detected a 28-mm-sized tumor. GISTs of the small intestine are sometimes associated with syndromic GISTs, such as type 1 neurofibromatosis and familial GIST syndrome [1]. However, in the present case, there were no clinical features of type 1 neurofibromatosis or a familial history of GIST. The findings of blood chemistry were within normal limits. A homogenous tumor (diameter, 28 × 28 mm) was detected on an abdominal computed tomography (CT) scan (Fig. 1a), while 18F-fluorodeoxyglucose positron emission tomography (FDG/PET) revealed a high accumulation at the same region (Fig. 1b). The maximum standard uptake value (SUV-max) was 5.5.

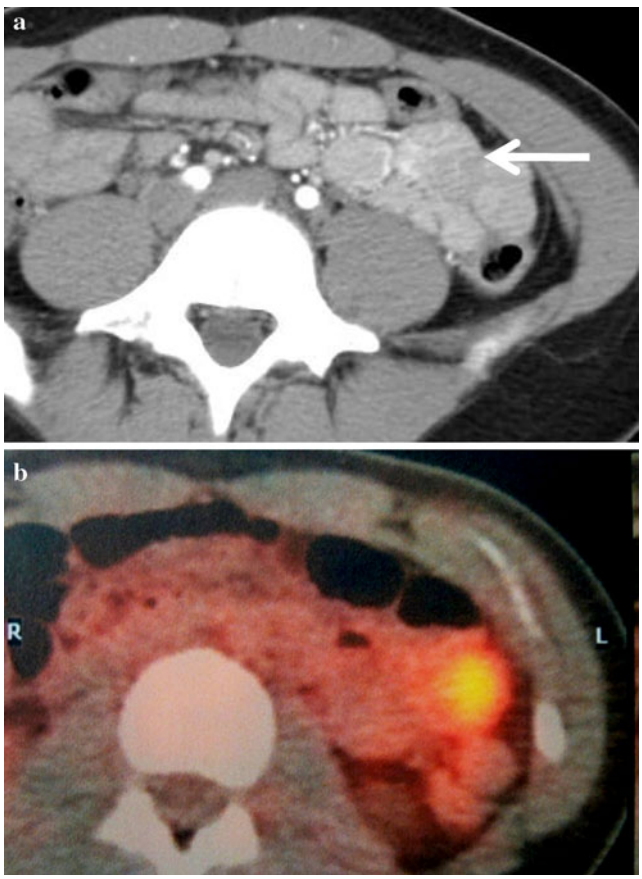

Fig. 1 **a** A homogenous tumor 28 × 28 mm in diameter was detected on an abdominal CT scan (*arrow*). **b** FDG/PET showed a high accumulation at the same region

Contrast radiography revealed a defect 30 mm in diameter in the jejunum. Double balloon enteroscopy was therefore performed; however, we were unable to detect the tumor. From these findings, we diagnosed the patient as having a GIST of the jejunum. During surgery, we first performed an exploratory laparoscopic examination and subsequently detected a tumor with clear margins (Fig. 2b). There was no evidence of swollen lymph nodes, liver metastases, or peritoneal disseminations. A wedge resection of the small intestine was then performed through a 4-cm transverse incision in the lower abdomen of the patient (Fig. 2a, c).

Hematoxylin–eosin staining revealed spindle cell morphology, but no epithelioid features. The findings of immunohistochemical analyses were positive for c-kit protein and CD34 (Fig. 3a, b) and negative for the expression of desmin and S-100 protein (Fig. 3c, d). Two mitoses were observed per 50 high-power fields (HPF) at an original magnification of 400×. The diagnosis of a low-grade GIST of the jejunum was confirmed in accordance with the risk assessment classification using size and the mitotic index [13]. A mutational analysis of the c-kit gene was performed by direct sequencing using genomic DNA obtained from a paraffin-embedded sample of the tumor tissue. The results revealed an internal tandem repeat of codons 502 and 503 in exon 9 of the c-kit gene (Fig. 4).

The patient's recovery was uneventful and there was no evidence of recurrence of the tumor 1 year after the operation.

Discussion

We present a rare case of pediatric GIST of the small intestine and summarize 11 other similar reported cases. GISTs are defined as mesenchymal tumors that arise from the gastrointestinal tract and occur primarily in adults. Neoplastic GIST cells appear to arise from a common precursor cell that develops into the interstitial cells of Cajal in the normal myenteric plexus. GISTs typically show overexpression of the c-kit protein and have activating mutations in the c-kit or PDGFRA genes [14]. The overall incidence of GISTs is low and is estimated to be 10–20 cases per million [1]. GISTs are most commonly located in the stomach (30–70%), followed by the small intestine (20–40%). It is known that GISTs of the small intestine show more aggressive behavior than gastric GISTs with similar characteristics [16]. GISTs in the pediatric population are extremely rare and account for only 1–2% of GIST cases [15]. Only 2.7% of GISTs of the stomach and 0.6% of GISTs of the small intestine occur before the age of 21 years [16]. Previously reported pediatric GISTs have occurred predominantly in girls and are present usually as multiple nodules in the stomach [2]. A MEDLINE search

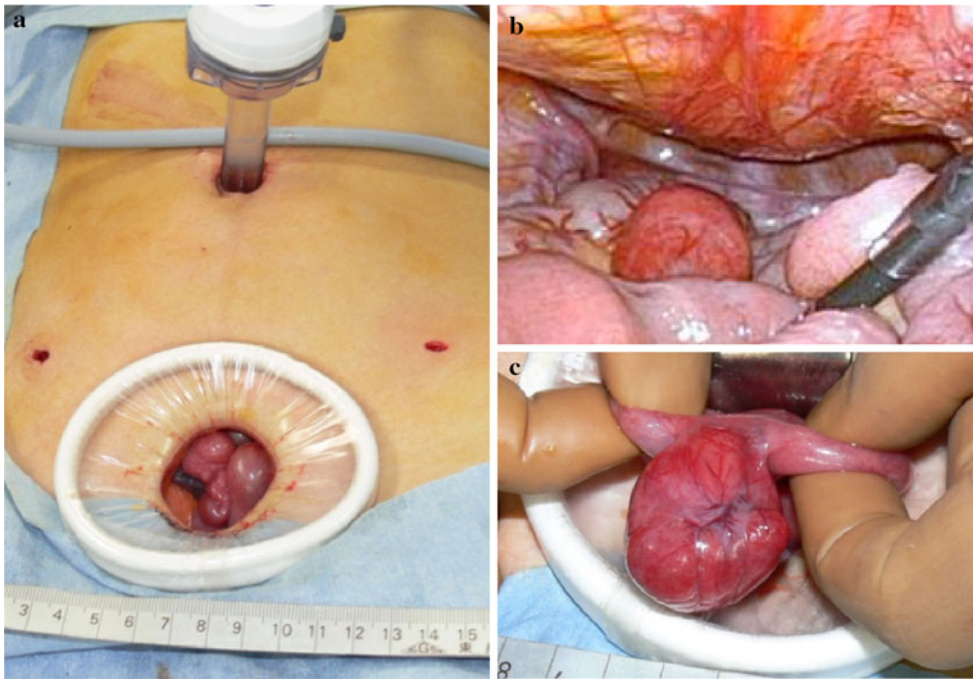

Fig. 2 **a**, **c** A wedge resection of the small intestine was performed through a 4-cm transverse incision in the lower abdomen of the patient. **b** A tumor with clear margins was detected by laparoscopic exploration

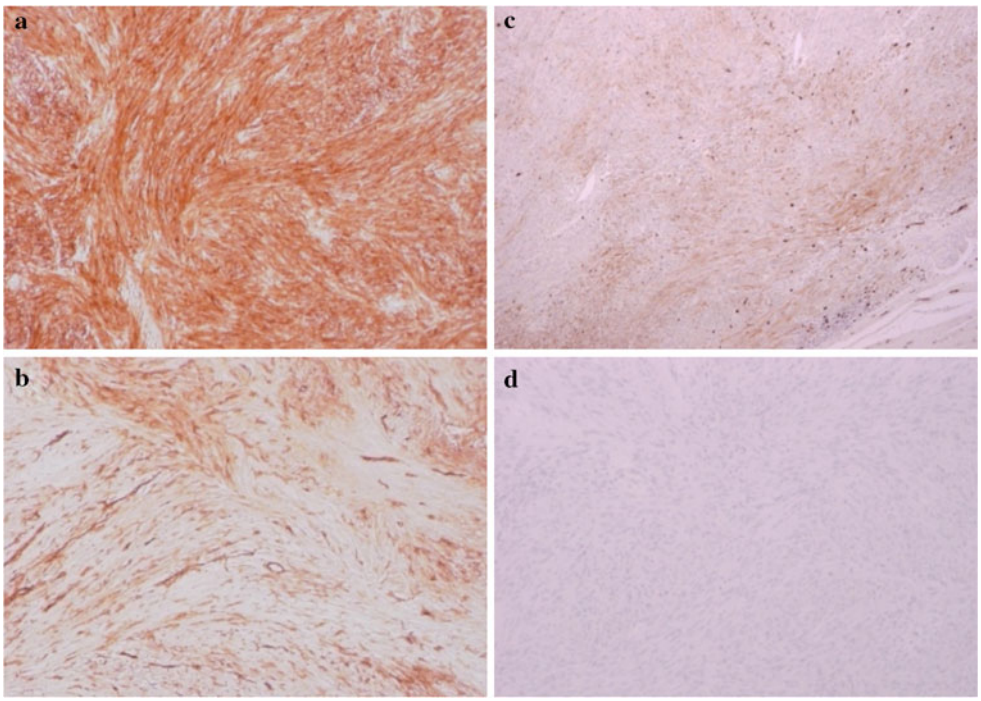

Fig. 3 Immunochemical analysis was positive for c-kit (**a**) and CD34 (**b**) (original magnification ×100). Desmin (**c**) and S-100 protein (**d**) were not expressed (original magnification ×100)

was conducted in July 2009 to obtain an overview of the literature on pediatric GISTs of the small intestine. The keywords used in the search were "gastrointestinal stromal tumor" accompanied by "young", "boy", "girl", "children", or "pediatric". To date, only 11 cases diagnosed as GIST of the small intestine in patients aged 18 years or younger have been reported in the English literature [3–12]. Although the gastrointestinal mesenchymal tumors identified prior to 1999 were mostly labeled as smooth muscle neoplasms before the c-kit staining procedure was developed, most of these tumors were classified as GISTs after 2000 [17]. For this reason, there were probably more than just a few cases of GISTs prior to 1999, according to the current diagnostic criteria of GIST. However, we cannot determine whether these cases were strictly classified as GIST cases. In this study, therefore, we analyzed the cases

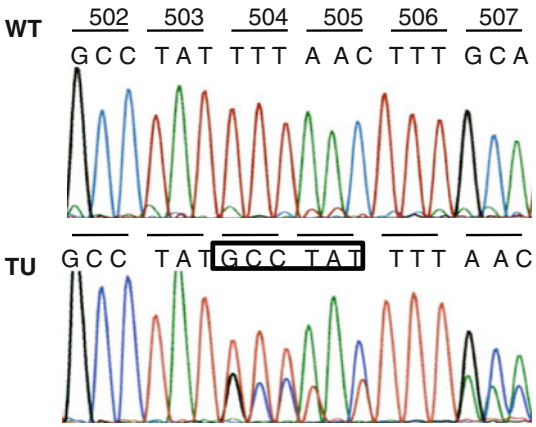

Fig. 4 Direct sequence analysis of selected coding sequences of the c-kit gene revealed an internal tandem repeat of codons 502 and 503 in exon 9. *WT* wild-type, *TU* tumor

confirmed as GIST by the current criteria based on histopathological and immunohistochemical examinations according to the methodology described in several published papers [10, 15, 18].

Recent studies have highlighted the differences between adult and pediatric GISTs, however, these previous analyses of pediatric cases primarily involved gastric tumors, and the clinicopathological characteristics of pediatric GISTs of the small intestine were not established. Table 1 summarizes the clinicopathological features of 12 cases of GISTs of the small intestine in patients aged 18 years or younger, including our case. These 12 cases comprised 8 male and 4 female patients with a median age of 9.5 years (range 0 days to 18 years). Tumor size ranged from 15 to 160 mm, and all cases involved single tumors. Two tumors were located in the duodenum (16.7%), while the other ten tumors were located in the jejunum and ileum (83.3%). GISTs of the small intestine are sometimes associated with syndromic GISTs, such as type 1 neurofibromatosis and familial GIST syndrome [1]. Neurofibromatosis is a multisystemic genetic disorder that is associated commonly with cutaneous, neurologic, and orthopedic manifestations. Multiple GIST tumors are usually observed in the proximal jejunum in patients with type 1 neurofibromatosis [18]. In addition, familial GIST syndrome is defined as a hereditary predisposition to develop GIST due to germline mutations in the c-kit or PDGFRA genes [1]. A total of only 21 cases of familial GIST have been reported previously [17]. It has been reported that GISTs in pediatric populations are not usually associated with a syndromic GIST. However, multiple, sometimes diffuse, GISTs in the small intestine typically develop during middle age in patient with syndromic GIST. There was no clinical history of neurofibrinomatosis or familial GIST syndrome among the 12 cases of GIST of the small intestine reviewed in this paper, and each case only involved one tumor.

Four patients initially presented with gastrointestinal bleeding and subsequent anemia, and three patients presented with intestinal obstruction. Generally, in adult case, detection of GISTs of the small intestine is more difficult than detection of gastric GISTs, and the most common presentation of GIST of the small intestine are gastrointestinal bleeding and intestinal obstruction [16]. Our findings revealed that the onset of this disease is similar in adult and pediatric populations. Two patients presented with abdominal pain, including the present case. In the present case, the abdominal pain was not severe, but it was persistent. Therefore, we conducted an abdominal ultrasonography and subsequently detected the tumor. Although primary solid tumors of the gastrointestinal tract are very rare in pediatric populations, we should keep this disease in mind when providing regular medical care even in case of mild but persistent abdominal pain in pediatric patients.

In general, the diagnoses of GIST were based on the histopathological and immunohistochemical criteria from the current standard definition of the disease [13]. Pathologically, epithelioid cell tumors or mixed spindle and epithelioid tumors are most common in pediatric cases of gastric GISTs, whereas spindle cell tumors are most common in adult cases of GISTs [19]. Detailed descriptions of the characteristics of the previously reported tumors showed that eight tumors had a pure spindle cell morphology (8/11, 72.7%), while the other three tumors consisted of mixed spindle and epithelioid cells (3/11, 27.2%). All the tumors were positive for the c-kit protein (10/10, 100%), while six tumors were positive for CD34 (6/9, 66.7%). The median mitotic index was 2.0 per 50 HPF (range 1–155). According to risk assessment classification, eight cases were classified as low grade (8/11, 72.7%), one case was classified as intermediate grade (1/11, 9.1%) and two cases were classified as high grade (2/11, 18.2%).

Fewer than 15% of pediatric gastric GISTs have c-kit or PDGFRA genes mutations, whereas 80% of adult GISTs have mutations in these genes [20]. Mutations have been detected in exon 9, 11, 13, and 17 of the c-kit gene in GISTs. Approximately 70–80% of GISTs have mutations in exon 11, and 10–20% have mutations in exon 9 of the c-kit gene. Several studies have reported a correlation between the nature of the molecular alterations of the c-kit gene and the response to imatinib treatment [21]. GISTs with the wild-type c-kit gene are likely to be resistant to imatinib treatment, compared to tumors with mutations in the c-kit gene. It has also been reported that GISTs with mutations in exon 9 of the c-kit gene are less sensitive to imatinib, compared to those with mutations in exon 11 of the c-kit gene [1]. As the majority of gastric GISTs in pediatric populations have the wild-type phenotype for the c-kit or PDGFRA genes, it would be expected that pediatric patients with gastric GISTs may have a poorer response to

Table 1 Clinicopathological, immunohistochemical, and genetic features of reported cases of GISTs of the small intestine in patients aged 18 years or younger, including the present case

Case	Author (year)	Age (year)	Sex	Symptom	Location	Size (mm)	Number	Mitotic index	Risk classification	c-kit	CD34	Desmin	S-100	Tumor type	c-kit/ PDGFRA mutation	Treatment	Prognosis (years)	Recurrence	Imatinib therapy
1	Wu [3]	0 (0 day)	Male	Intestinal obstruction	Small intestine (jejunum)	35	1	5/50 HPF	Low	+	+	−	ND	S + E	ND	Operation	1.0 NED	−	−
2	Bates [4]	0 (14 day)	Female	Intestinal obstruction	Small intestine (jejunum)	15	1	10/50 HPF	Medium	+	−	−	+	S + E	ND	Operation	1.0 NED	−	−
3	Shenoy [5]	0 (1 day)	Male	Intestinal obstruction	Small intestine (ileum)	25	1	1/10 HPF	Low	ND	+	ND	−	S	ND	Operation	1.0 NED	−	−
4	Cypriano [6]	4.3	Male	ND	Small intestine	160	1	115/50 HPF	High	ND	ND	ND	ND	S	ND	Operation	1.2 DOD	Local recurrence	ND
5	Cypriano [6]	0.25	Female	ND	Small intestine	60	1	155/50 HPF	High	+	+	ND	ND	S	ND	Operation	1.6 DOD	Liver	ND
6	Towu [7]	7	Male	Melena	Duodenum	20	1	1/10 HPF	Low	+	−	ND	−	S	ND	Operation	NED	−	−
7	Chiarugi [8]	14	Male	Melena	Duodenum	40	1	<5/50 HPF	Low	+	−	ND	−	E + S	WT	Operation	NED	−	−
8	Viola [9]	14	Male	Anemia	Small intestine (jejunum)	25	1	Low	Low	+	ND	ND	ND	ND	ND	Operation	2.0 NED	−	−
9	Agaram [10]	17	Male	ND	Small intestine	ND	1	1/50 HPF	ND	+	ND	ND	ND	S	KIT exon 11	Operation	22 NED	−	−
10	Bauer [11]	17	Male	Melena	Small intestine (jejunum)	31	1	1/50 HPF	Low	+	+	−	−	S	KIT exon 11	Operation	1.2 NED	−	−
11	Migliorati [12]	12	Female	Abdominal pain	Small intestine (ileum)	40	1	2/50 HPF	Low	+	+	−	−	S	ND	Operation	4.0 NED	−	−
12	Present case	18	Female	Abdominal pain	Small intestine (jejunum)	28	1	2/50 HPF	Low	+	+	−	+	S	KIT exon 9	Operation	1.0 NED	−	−

S spindle cell type, *E* epithelial cell type, *NED* no evidence of disease, *DOD* died of disease, *ND* not described

imatinib treatment than adult GISTs. Of the 12 cases reviewed, gene mutational analyses were performed in four cases. Among these four cases, one had a wild-type phenotype for the c-kit and PDGFRA genes (25.0%), two had a mutation in exon 11 (50.0%), and one had a mutation in exon 9 of the c-kit gene (25.0%, present case). Although gene mutational analysis was carried out in only 4 of the 12 cases, it appears likely that pediatric patients with GISTs of the small intestine may have a high frequency of c-kit gene mutations as compared to cases of pediatric gastric GISTs.

In summary, pediatric GISTs arising from the small intestine are extremely rare. Previous cases of pediatric GISTs primarily involved gastric tumors, and therefore the clinicopathological characteristics of pediatric GISTs of the small intestine have not yet been elucidated. This report suggests that pediatric GISTs of the small intestine do not display the previously reported features of pediatric gastric GISTs, but instead have the features of adult GISTs. In pediatric populations, GISTs of the small intestine tend to harbor a mutation in the c-kit gene and thus differ from gastric GISTs, therefore, GISTs of the small intestine are expected to show a better response to imatinib treatment than gastric GISTs in this population. This finding has important implications for deciding the treatment strategy for pediatric patients with GISTs. Few previous reports of GISTs of the small intestine exist where gene mutational analyses was performed. Further investigations are required to clarify the relation between the alterations in the c-kit gene and the response to imatinib treatment in pediatric patients with GISTs of the small intestine.

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