Case Report:

Gastrointestinal Stromal Tumors of the Small Intestine in Pediatric Populations: A Case Report and Literature Review

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Running title: GIST of the Small Intestine in Pediatric Populations

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Key words: gastrointestinal stromal tumor, small intestine, pediatric populations, the c-kit gene mutation

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

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.

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. A 28-mm-sized tumor was subsequently detected by abdominal ultrasonography. 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-fluorodeoxy-glucose 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. 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 a 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 one 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 was conducted in July 2009 to obtain an overview of the literature on pediatric GISTs of the small intestine. The keywords used in the serch were "gastrointestinal stromal tumor" accompanied by "young," "boy," "girl," "children," or "pediatric." To date, only eleven cases diagnosed as GIST of the

small intestine in patients aged 18 years or younger have been reported in the English literature [3□12]. 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 10 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 [17]. 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 fistory 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.

In general, the diagnoses of GIST were based on the histopathological and immunohistochemical criteria that 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 [18]. Detailed descriptions of the characteristics of the previously reported tumors showed that 8 tumors had a pure spindle cell morphology (8/11, 72.7%), while the other 3 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 6 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, 8 cases were classified as low grade (8/11, 72.7%), 1 case was classified as intermediate grade (1/11, 9.1%) and 2 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 [19]. 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 [20]. 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 imatinib treatment than adult GISTs. Of the 12 cases reviewed, gene mutational analyses were performed in 4 cases. Among these 4 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. The number of reported cases of pediatric GISTs of the small intestine is limited, and therefore further investigations including gene mutational analyses are required.

References

1. Miettinen M, Lasota J (2006) Gastrointestinal stromal tumors: review on morphology, molecular pathology, prognosis, and differential diagnosis. Arch Pathol Lab Med 130:1466-1478.

2. Miettinen M, Lasota J, Sobin LH (2005) Gastrointestinal stromal tumors of the stomach in children and young adults: a clinicopathologic, immunohistochemical, and molecular genetic study of 44 cases with long-term follow-up and review of the literature. Am J Surg Pathol 29:1373-1381.

3. Wu SS, Buchmiller TL, Close P, Gershman GB, Peng SK, French SW (1999) Congenital gastrointestinal pacemaker cell tumor. Arch Pathol Lab Med 123:842-845.

4. Bates AW, Feakins RM, Scheimberg I (2000) Congenital gastrointestinal stromal tumour is morphologically indistinguishable from the adult form, but does not express CD117 and carries a favourable prognosis. Histopathology 37:316-322.

5. Shenoy MU, Singh SJ, Robson K, Stewart RJ (2000) Gastrointestinal stromal tumor: a rare cause of neonatal intestinal obstruction. Med Pediatr Oncol 34:70-71.

6. Cypriano MS, Jenkins JJ, Pappo AS, Rao BN, Daw NC (2004) Pediatric gastrointestinal stromal tumors and leiomyosarcoma. Cancer 101:39-50.

7. Towu E, Stanton M (2006) Gastrointestinal stromal tumour presenting with severe bleeding: a review of the molecular biology. Pediatr Surg Int 22:462-464.

8. Chiarugi M, Galatioto C, Lippolis P, Zocco G, Seccia M (2007) Gastrointestinal stromal tumour of the duodenum in childhood: a rare case report. BMC Cancer 7:79.

9. Viola S, Dray X, Boudjemaa S, Meklati M, Challier P, Kotobi H, Tounian P, Girardet JP, Vahedi K (2007) Pediatric jejunal gastrointestinal stromal tumor diagnosed by wireless capsule endoscopy. J Pediatr Gastroenterol Nutr 45:358-360.

10. Agaram NP, Laquaglia MP, Ustun B, Guo T, Wong GC, Socci ND, Maki RG, DeMatteo RP, Besmer P, Antonescu CR (2008) Molecular characterization of pediatric gastrointestinal stromal tumors. Clin Cancer Res 14:3204-3215.

11. Bauer TM, Berlin JD (2008) A 17 year-old man with an exon 11 mutation of CD-117 causing a gastrointestinal stromal tumor. Cancer Invest 26:182-184.

12. Migliorati R, Boccia G, Miele E, Avilia S, Pettinato G, Staiano A (2008) Gastrointestinal stromal tumor of the small bowel in a 12-year-old girl. J Pediatr Gastroenterol Nutr 47:667-669.

13. Fletcher CD, Berman JJ, Corless C, Gorstein F, Lasota J, Longley BJ, Miettinen M, O'Leary TJ, Remotti H, Rubin BP, Shmookler B, Sobin LH, Weiss SW (2002) Diagnosis of gastrointestinal stromal tumors: A consensus approach. Hum Pathol 33:459-465.

14. Hirota S, Isozaki K, Moriyama Y, Hashimoto K, Nishida T, Ishiguro S, Kawano K, Hanada M, Kurata A, Takeda M, Muhammad Tunio G, Matsuzawa Y, Kanakura Y, Shinomura Y, Kitamura Y (1998) Gain-of-function mutations of c-kit in human gastrointestinal stromal tumors. Science 279:577-580.

15. Kaemmer DA, Otto J, Lassay L, Steinau G, Klink C, Junge K, Klinge U, Schumpelick V (2009) The Gist of literature on pediatric GIST: review of clinical presentation. J Pediatr Hematol Oncol 31:108-112.

16. Miettinen M, Makhlouf H, Sobin LH, Lasota J. Gastrointestinal stromal tumors of the jejunum and ileum: a clinicopathologic, immunohistochemical, and molecular genetic study of 906 cases before imatinib with long-term follow-up (2006) Am J Surg Pathol 30:477-489.

17. Benesch M, Wardelmann E, Ferrari A, Brennan B, Verschuur A (2009 Gastrointestinal stromal tumors (GIST) in children and adolescents: A comprehensive review of the current literature. Pediatr Blood Cancer 53:1171-1179.

18. Prakash S, Sarran L, Socci N, DeMatteo RP, Eisenstat J, Greco AM, Maki RG, Wexler LH, LaQuaglia MP, Besmer P, Antonescu CR (2005) Gastrointestinal stromal tumors in children and young adults: a clinicopathologic, molecular, and genomic study of 15 cases and review of the literature. J Pediatr Hematol Oncol 27:179-187.

19. Janeway KA, Liegl B, Harlow A, Le C, Perez-Atayde A, Kozakewich H, Corless CL, Heinrich MC, Fletcher JA (2007) Pediatric KIT wild-type and platelet-derived growth factor receptor alpha-wild-type gastrointestinal stromal tumors share KIT activation but not mechanisms of genetic progression with adult gastrointestinal stromal tumors. Cancer Res 67:9084-9088.

20. Heinrich MC, Corless CL, Demetri GD, Blanke CD, von Mehren M, Joensuu H, McGreevey LS, Chen CJ, Van den Abbeele AD, Druker BJ, Kiese B, Eisenberg B, Roberts PJ, Singer S, Fletcher CD, Silberman S, Dimitrijevic S, Fletcher JA (2003) Kinase mutations and imatinib response in patients with metastatic gastrointestinal stromal tumor. J Clin Oncol 21:4342-4349.

Figure Legends:

Fig. 1a: A homogenous tumor 28×28 mm in diameter was detected on an abdominal CT scan (arrow).

Fig. 1b: FDG/PET showed a high accumulation at the same region.

Fig. 2a, c: A wedge resection of the small intestine was performed through a 4□cm transverse incision in the lower abdomen of the patient.

Fig. 2 b: A tumor with clear margins was detected by laparoscopic exploration.

Fig. 3a, b: Immunochemical analysis was positive for c-kit (**A**) and CD34 (**B**) (original magnification×100).

Fig. 3 c, d: Desmin (**C**) and S-100 protein (**D**) were not express (original magnification×100).

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.

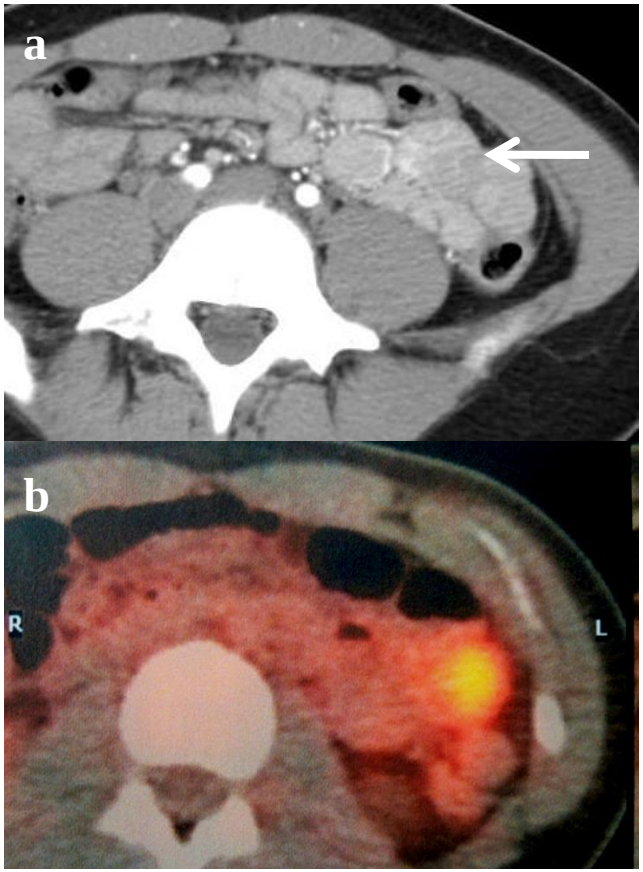
WT: Wild-type, TU: Tumor

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 theraphy
1	Wu, S.W. (1999) [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, A. W. (2000) [4]	0 (14day)	female	intestinal obstruction	small intestine(jejunum)	15	1	10/50 HPF	medium	+	-	-	+	S+E	ND	operation	1.0 NED	-	-
3	Shenoy, M.U. (2000) [5]	0 (1day)	male	intestinal obstruction	small intestine(ileum)	25	1	1/10 HPF	low	ND	+	ND	-	S	ND	operation	1.0 NED	-	-
4	Cypriano, M.S. (2004) [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, M.S. (2004) [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, E. (2006) [7]	7	male	melena	duodenum	20	1	1/10 HPF	low	+	-	ND	-	S	ND	operation	NED	-	-
7	Chiarugi, M. (2007) [8]	14	male	melena	duodenum	40	1	<5/50 HPF	low	+	-	ND	-	E+S	WT	operation	NED	-	-
8	Viola, S. (2007) [9]	14	male	anemia	small intestine(jejunum)	25	1	low	low	+	ND	ND	ND	ND	ND	operation	2.0 NED	-	-
9	Agaram, N.P. (2008) [10]	17	male	ND	small intestine	ND	1	1/50 HPF	ND	+	ND	ND	ND	S	KIT exon 11	operation	22 NED	-	-
10	Bauer, T.M. (2008) [11]	17	male	melena	small intestine (jejunum)	31	1	1/50 HPF	low	+	+	-	-	S	KIT exon 11	operation	1.2 NED	-	-
11	Migliorati, R. (2008) [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

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



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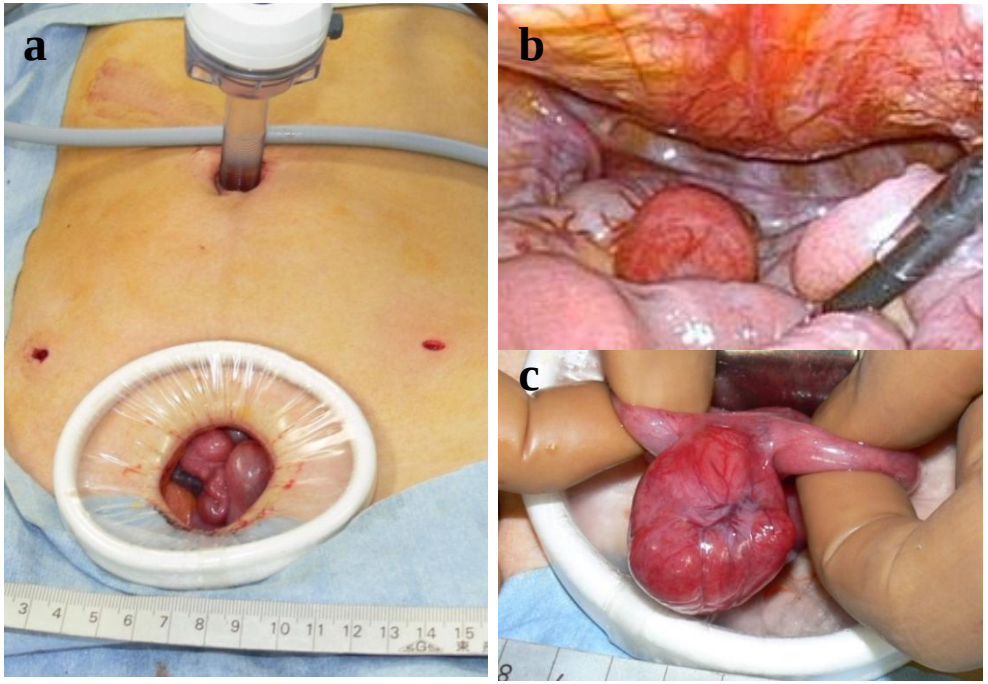
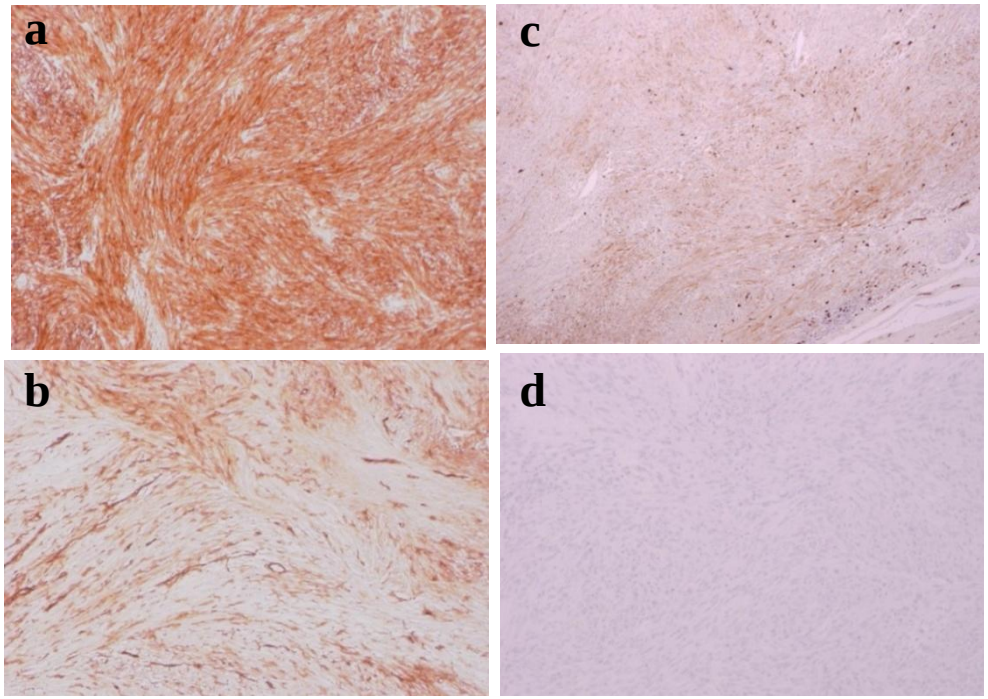


Fig. 3: Immunochemical analysis was positive for c-kit (**a**) and CD34 (**b**) (original magnification × 100).
Desmin (**c**) and S-100 protein (**d)** were not express (original magnification × 100).



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