Gastrointestinal Stromal Tumors Presenting as Surgical Emergencies: A Six-Patient Case Series

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Abstract: Aim: To evaluate surgical and oncologic outcomes of patients who underwent urgent exploratory laparotomy, and successful surgical resection of gastrointestinal stromal tumors.

Methods: Medical records were retrospectively searched from January 2005 to January 2012 for cases with gastrointestinal stromal tumors, who had undergone urgent exploratory laparotomy.

Results: Of 51 patients operated for GISTs from January 2005 to January 2012, 6 cases had undergone urgent exploratory laparotomy and surgical resection. Our study group consisted of 4 female (66.6 %) and 2 male (33.4 %) patients with a median age of 60 years (range: 35-76 yrs). Their tumors were located in the stomach (n=1), jejunum (n=2), ileum (n=2), and rectum (n=1). For these tumors, total gastrectomy (n=1), segmental resection of the jejunum (n=2) or ileum (n=2), and left hemicolectomy (n=1) were performed followed by an uneventful postoperative course in all patients. According to Fletcher criteria, five tumors (83.3%) were classified as intermediate and high risk. No postoperative morbidity and mortality were noted. All patients received postoperative treatment with a tyrosine kinase inhibitor, imatinib. Median length of the hospital stay was 8 (range: 6 to 12) days. With a median follow-up of 32 (range 3 to 64) months, disease-free survival rate was 100 percent.

Conclusions: Although quite rare, patients with gastrointestinal stromal tumors may suffer from occult gastrointestinal hemorrhage and abdominal pain as the first clinical manifestations leading to urgent exploratory laparotomy and surgical extirpation of the tumor.

Keywords: Gastrointestinal stromal tumor, GIST, emergency, urgent laparotomy.

INTRODUCTION

Gastrointestinal stromal tumors (GISTs) are rare neoplasms which account for 0.1–3% of all gastrointestinal malignancies, but 80% of all gastrointestinal mesenchymal tumors [1-3]. Because of their histological features resembling uterine tumors, they were misdiagnosed as leiomyomas or leiomyosarcomas [4]. Nowadays there is compelling ultrastructural and immunohistochemical evidence demonstrating that these lesions can exhibit neural ganglionic and neural-myoid histological features [4].

Peak incidence of GIST is observed in patients older than 50 years of age [2, 3]. A GIST can be located anywhere along the gastrointestinal tract. GISTs are most commonly located in the stomach and small intestine, with only 5%-10% of them arising in the colon and rectum [5]. Small GISTs are usually asymptomatic, but as the tumor grows, vague symptoms develop, such as abdominal discomfort, pain, bloating, or signs of an abdominal mass or anemia secondary to overt or occult bleeding [5]. Ten-year survival rates range between 50 and 70%, depending on specific prognostic factors [6].

Normally, gastrointestinal bleeding secondary to GISTs becomes more severe with time leading to chronic anemia [7]. The severity of the hemorrhage, which requires urgent surgical control, might be considered unusual for this sort of tumor. The aim of this study was to evaluate surgical and oncologic outcomes of patients who underwent urgent exploratory laparotomy, and successful surgical resection of GISTs.

MATERIALS AND METHODS

Medical records requested from Haseki Training and Research Hospital, Department of General Surgery were retrospectively searched from January 2005 to January 2012 for cases with GIST, who had undergone urgent exploratory laparotomy. Pathologists confirmed histologic diagnosis of all tumors (Figure **1a**, **1b**). Also all patients' pathologic diagnosis was verified by CD117 (C-kit). All patients were C-Kit positive. According to Fletcher criteria, tumors of less than 2 cm in diameter and with a mitotic count (MC) of less than 5 per 50 high-power fields on microscopic examination (HPFs) were classified as very low risk [5]. Low risk

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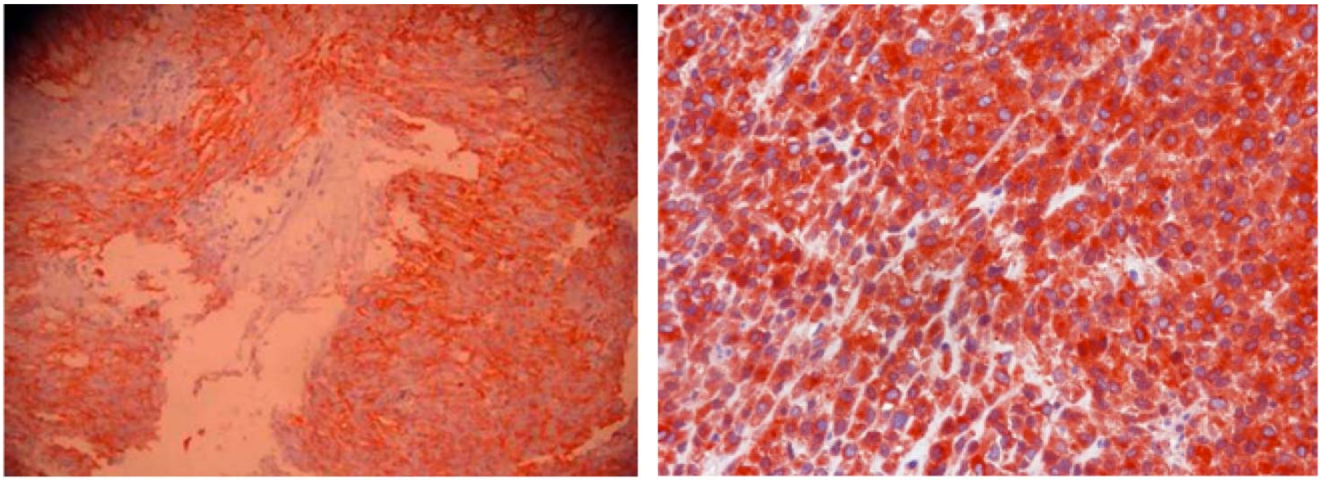

a **b**

Figure 1: a. C-kit was strongly positive in all patients. Hematoxylin and eosin, 40 × 10.
b. Small bowel GIST. Immunostaining for GIST (CD 117 staining, DAKO, 200X magnification).

Table 1: GISTs Classification by Fletcher *et al*. [5]

Risk of malignancy	Size of tumor (cm)	Mitotic counts (/50HPF)
Very low	< 2	< 5 / 50
Low	2 – 5	< 5
Intermediate	< 5	6 – 10
	5 – 10	< 5
High	> 5	> 5
	> 10	Any counts
	Any size	> 10

was assigned for a GIST ranged from 2 to 5 cm and the MC was less than 5 per 50 HPFs. A GIST less than 5 cm in diameter with 6-10 MCs per 50 HPFs or those measuring 5-10 cm with < 5 MC per 50 HPFs were included in the intermediate risk category. Finally GISTs larger than 10 cm with > 10 MCs per 50 HPS or those bigger than 5 cm with > 5 MCs per 50 HPFs were considered as high- risk tumors (Table **1**).

Postoperative follow-up was carried out through routine visits at our outpatient clinic. Investigations consisted of double balloon enteroscopy, computed tomography and, colonoscopy.

RESULTS

Of 51 patients operated for GISTs from January 2005 to January 2012, 6 cases had undergone urgent exploratory laparotomy and surgical resection (Table **2**). Our study group consisted of 4 female (66.6 %) and 2 male (33.4 %) patients with a median age of 60 years (range: 35-76 yrs). Their tumors were located in the stomach (n=1) (Figure **2**), jejunum (n=2), ileum (n=2), and rectum (n=1). For these tumors, total gastrectomy (n=1), segmental resection of the jejunum (n=2) or ileum (n=2), and low anterior resection (n=1) were performed followed by an uneventful postoperative course in all patients. According to Fletcher criteria, 5 tumors (83.3%) were classified as intermediate and high risk. No postoperative morbidity and mortality were noted. No patient experienced an anastomotic stricture. All patients received postoperative treatment with a tyrosine kinase inhibitor, imatinib. Median length of the hospital stay was 8 (range: 6 to 12) days. With a median follow-up of 32 (range 3 to 64) months, disease-free survival rate was 100 percent.

DISCUSSION

The current study was a case series of six patients had undergone urgent exploratory laparotomy for GIST with promising short- and middle-term outcomes.

Peak incidence of GIST is encountered in patients older than 50 years of age, and only about 5% of GIST

Table 2: Patient Demographics and Complaints

No	Sex	Age	Symptoms	Localization of the tumor	Operation	Tumor size (cm)	Histopathological Subtype	Fletcher Criteria	Length of stay (days)	Follow-up (months)
1	M	43	Abdominal pain, lower GIS bleeding	Rectum	Left hemicolectomy	6x4	Epitheloid	Low risk	12	45
2	F	65	Abdominal pain, upper GIS bleeding, hemorrhagic shock	Stomach	Total gastrectomy	7x5	Spindle Cell	Intermediate risk	7	36
3	F	76	Abdominal pain, lower GIS bleeding	Ileum	Segmental resection of the ileum	15x10	Epitheloid	High risk	9	26
4	F	35	Lower GIS bleeding	Jejunum	Segmental resection of the jejunum	4x3	Epitheloid	Intermediate risk	6	28
5	M	55	Abdominal mass, lower GIS bleeding	Jejunum - transverse colon	Segmental resection of the jejunum and the transverse colon	10x12	Spindle Cell	High risk	8	64
6	F	71	Abdominal pain, lower GIS bleeding	Ileum	Segmental resection of the ileum	8x6	Epitheloid	Intermediate risk	8	3

M= Male; F= Female; GIS= Gastrointestinal.

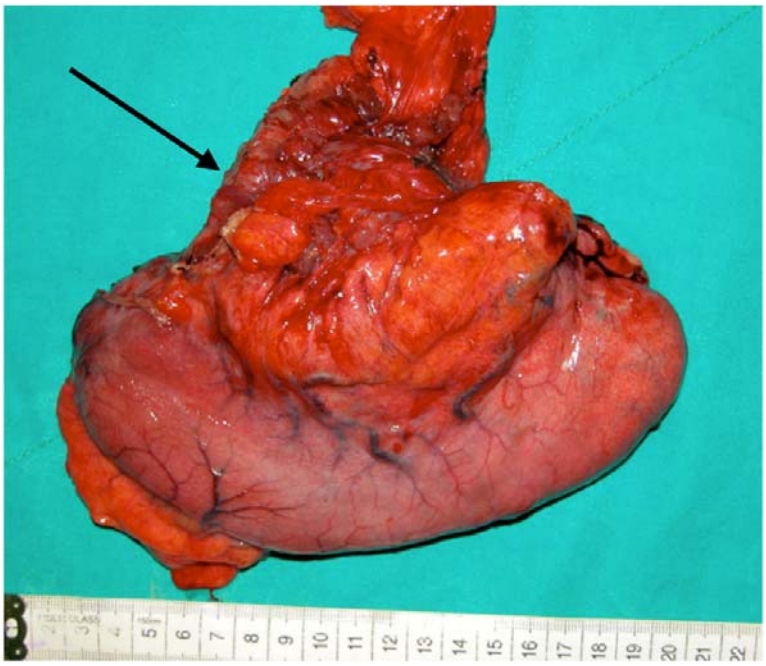

Figure 2: Gastric GIST invasing the hepatogastric ligament. Arrow shows the tumor.

patients are younger than 30 years [2, 3]. In our series, median age was 60 years, compliant with the literature. The clinical presentation of a GIST is primarily dependent on the site of its origin and shows exceptional variability [2]. Signs and symptoms are usually nonspecific and do not manifest until the tumor has reached to a considerable size. These patients may experience anorexia, abdominal pain, weight loss,

anemia from occult bleeding or symptoms of intestinal obstruction [2, 8]. Intractable bleeding, which requires urgent surgical control, is rarely encountered in cases with GIST.

In general, traditional endoscopy is the first step in the diagnosis of GISTs [2]. About 63% of these cases have been identified incidentally through endoscopic screening, with 85% of these originating in the stomach [9]. Typical endoscopic sign of a GIST is an endophytic polypoid submucosal mass protruding toward the mucosa, sometimes with surface ulcerations. All of our patients were operated because of acute abdomen or mechanical intestinal obstruction and diagnosis were made postoperatively. In our series, GISTs were located in the jejunum (n=2), ileum (n=2), rectum (n=1) and stomach (n=1).

Surgery remains the standard of care for GISTs and the surgical treatment of choice should be radical extirpation of the tumor as a whole [10]. Partial resection must only be performed in case of large tumors, for palliative purposes or for the control of symptoms or complications such as compression of other organs, hemorrhage, or pain [10, 11]. Systemic lymph node dissection is not recommended by many authors [11, 12]. In our study, we were able to achieve a complete resection, in each case, with an intact surgical margin. For our cases we performed total gastrectomy, segmental resection of the jejunum, segmental resection of the ileum and low anterior resection.

Histopathologically, most GISTs consist of spindle tumor cells, and immunohistochemical staining usually reveals KIT positivity [5]. However, epithelioid histology is found in about 20% of all GISTs [5, 13]. In such cases, an immunohistochemically positive result for KIT is a useful diagnostic marker, although epithelioid GISTs have been reported to lack the c-kit gene mutation. Most KIT negative GISTs have epithelioid histology, and these histologic findings are sometimes difficult to discern. Further immunohistochemical analysis may be needed, and genetic studies investigating the presence mutation of the c-kit and PDGFRA genes may be helpful for the diagnosis [13]. Based on the histologic and immunohistochemical results, we diagnosed epithelioid type in 4 patients, and spindle cell type in 2 patients.

Until recently, recurrent and metastatic GISTs have had fatal outcomes, as response rates to conventional chemotherapy were <5%. The substance STI571 i.e. imatinib (Gleevec, Novartis, Basel, Switzerland), was recently found to act as a powerful selective inhibitor of tyrosinekinases (c-ABL, bcr-ABL), PDGFR (platelet derived growth factor) receptor and c-kit receptor. Imatinib is well tolerated by oral administration, and the suggested efficient dose must be >300 mg per day to achieve curative results [14]. All patients in our series received postoperative treatment with the tyrosine kinase inhibitor, imatinib.

Ten-year survival rates range between 50% and 70%, depending on specific prognostic factors [6]. About 40% of the patients with primary GISTs who had complete resection were reported to have a recurrent disease. Within a median follow up of 24 months, mostly local recurrences or liver metastases have been cited [2, 3, 6]. The main prognostic factor for GISTs is the mitotic count. A prognostic classification was defined by Fletcher *et al.* which has been widely accepted and used today (Table **1**) [5]. According to Fletcher criteria, 5 tumors (83.3%) were classified as intermediate or high risk in our series. With a median follow-up of 32 months (range, 3–64), disease-free survival rate was 100 percent.

This study had a couple of limitations which deserve some comments. Firstly, the sample was small, with six patients enrolled. However, so far, this is the first series to report the results of patients undergoing urgent exploratory laparotomy for GISTs.

CONCLUSION

Although an unusual neoplasm, GIST should be remembered as a cause of gastrointestinal hemorrhage leading to urgent exploratory laparotomy. During operation, surgeon must be prepared to recognize malignant lesions with the purpose of managing them correctly. Appropriate operation depends on factors as general conditions of the patient, urgency of the condition, size and location of the tumor as well as suspicion of malignancy.

CONFLICT OF INTEREST

None of the authors has conflict of interest with the submission.

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MEETING PRESENTATION

None.

REFERENCES

[1] Miettinen M, Lasota J. Gastrointestinal stromal tumors: Review on morphology, molecular pathology, prognosis, and differential diagnosis. Arch Pathol Lab Med 2006; 130: 1466-78.

[2] Scarpa M, Bertin M, Ruffolo C, Polese L, D'Amico DF, Angriman I. A systematic review on the clinical diagnosis of gastrotintestinal stromal tumor. J Surg Oncol 2008; 98: 384-92. http://dx.doi.org/10.1002/jso.21120

[3] Miettinen M, Lasota J. Gastrointestinal stromal tumors - definition, clinical, histological, immunohistochemical, and molecular genetic features and differential diagnosis. Virchows Arch 2001; 438: 1-12. http://dx.doi.org/10.1007/s004280000338

[4] Lev D, Kariv JI, Issakov J, Merhav H, Berger E, Merimsky J, *et al*. Gastrointestinal stromal sarcomas. Br J Surg 1999; 86: 545-9. http://dx.doi.org/10.1046/j.1365-2168.1999.01075.x

[5] Fletcher CD, Berman JJ, Corless C, Gorstein F, Lasota J, Longley BJ, *et al*. Diagnosis of gastrointestinal stromal tumors: A consensus approach. Hum Pathol 2002; 33: 459-65. http://dx.doi.org/10.1053/hupa.2002.123545

[6] Emory TS, Sobin LH, Lukes L, Lee DH, O´Leary TJ. Prognosis of gastrointestinal smooth-muscle (stromal) tumors: dependence on anatomic site. Am J Surg Pathol 1999; 23: 82-7. http://dx.doi.org/10.1097/00000478-199901000-00009

[7] Morgan BK, Compton C, Talbert M, Gallagher WJ, Wood WC. Benign smooth muscle tumors of the gastrointestinal tract. Ann Surg 1990; 211: 63. http://dx.doi.org/10.1097/00000658-199001000-00011

[8] Miettinen M, Majidi M, Lasota J. Pathology and diagnostic criteria of gastrointestinal stromal tumors (GISTs): a review. Eur J Cancer 2002; 38: S39-51. http://dx.doi.org/10.1016/S0959-8049(02)80602-5

[9] Hasegawa T, Matsuno Y, Shimoda T, Hirohashi S. Gastrointestinal stromal tumor: consistent CD117 immunostaining for diagnosis, and prognostic classifi cation based on tumor size and MIB-1 grade. Hum Pathol 2002; 33: 669-79. http://dx.doi.org/10.1053/hupa.2002.124116

[10] Biasco G, Velo D, Angriman I, Astorino M, Baldan A, Baseggio M, *et al*.; Section of Oncology of the Italian Society of Gastroenterology; Interdisciplinary GIST Group-G.I.GIST, Veneto Institute of Oncology IOV-IRCCS Azienda Ospedale, University of Padua; GIST Study Group, Bologna University. Gastrointestinal stromal tumors: Report of an audit and review of the literature. Eur J Cancer Prev 2009; 18: 106-16. http://dx.doi.org/10.1097/CEJ.0b013e32830c8da8

[11] Chen TW, Liu HD, Shyu RY, Yu JC, Shih ML, Chang TM, Hsieh CB. Giant malignant gastrointestinal stromal tumors: recurrence and effects of treatment with STI-571. World J Gastroenterol 2005; 11: 260-63.

[12] Aparicio T, Boige V, Sabourin JC, Crenn P, Ducreux M, Le Cesne A, Bonvalot S. Prognostic factors after surgery of primary resectable gastrointestinal stromal tumors. Eur J Surg Oncol 2004; 30: 1098-103. http://dx.doi.org/10.1016/j.ejso.2004.06.016

[13] Sakurai S, Hasegawa T, Sakuma Y, Takazawa Y, Motegi A, Nakajima T, *et al*. Myxoid epithelioid gastrointestinal stromal tumor (GIST) with mast cell infi ltrations: a subtype of GIST with mutations of platelet-derived growth factor receptor alpha gene. Hum Pathol 2004; 35: 1223-30. http://dx.doi.org/10.1016/j.humpath.2004.07.008

[14] Verweij J, Casali PG, Zalcberg J, LeCesne A, Reichardt P, Blay JY, *et al*. Progression-free survival in gastrointestinal stromal tumors with high-dose imatinib: randomised trial. Lancet 2004; 364: 1127-34. http://dx.doi.org/10.1016/S0140-6736(04)17098-0

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