Primary Jejunal Gastrointestinal Stromal Tumor: Diagnosis Delay of 3 Years but Successful Management in Early Stage (II) by Surgery and Adjuvant Therapy

Ferdous Ara Begum a  Md Arifur Rahman b  Hashim Rabbi c  Golam Mostofa d  Qamruzzaman Chowdhury b

a Department of Medical Oncology, National Institute of Cancer Research and Hospital, Dhaka, Bangladesh; b Department of Oncology, Bangladesh Specialized Hospitals, Dhaka, Bangladesh; c Department of Surgery, BRB Hospitals Limited, Dhaka, Bangladesh; d Anowara Medical Services, Dhaka, Bangladesh

Keywords
Jejunum · Gastrointestinal stromal tumor · Primary treatment · Adjuvant therapy · Imatinib

Abstract
In the digestive system, mesenchymal origin of tumors is quite rare; in general, they are recognized as gastrointestinal stromal tumors (GISTs). The incidence of GISTs is very low (2 in 100,000), while jejunal GISTs are extremely rare, accounting for 0.1–3% of all gastrointestinal (GI) tumors. Small intestinal GISTs are the second most common (25%) site in the GI tract, usually occurring in the duodenum. We present the case of a 62-year-old Bangladeshi female with a history of GI bleeding 3 years earlier; the cause of the bleeding had not been found despite extensive investigations. In the meantime, the patient had developed occasional abdominal pain and lumpy feelings in the right side of the abdomen without any GI bleeding. Exploratory laparotomy was carried out in view of a small intestinal mesenteric mass in a computed tomography scan. On midline incision there was a 6 × 6 cm mass in the antimesenteric border of the jejenum approximately 30 cm from the duodenojejunal flexure, which was resected followed by anastomosis. The presentation of GISTs ranges from asymptomatic to mild abdominal pain and mass (5–50%) and mechanical obstruction (5%) as well as hemorrhage – perforation having rarely been reported (0.8%) – making the diagnosis difficult. Exophytic growth of these tumors has been noted in 18–30% of cases. In view of intermediate risk of malignancy, the patient was started with adjuvant imatinib 400 mg once daily due to probability of disease recurrence (24%).
Introduction

In the digestive system, from mouth to anus, mesenchymal origin of tumors is quite rare; in general, they are recognized as gastrointestinal stromal tumors (GISTs). The incidence of GISTs in the alimentary tract is very low (2 in 100,000) and is about 1% of all gastrointestinal (GI) malignancies [1]. However, jejunal GIST is extremely rare, accounting for 0.1–3% of all GI tumors [2]. The stomach is the main site of presentation (two-thirds) [3], followed by the small intestine (one-fourth), usually the duodenum [4]. There is a minimal male predominance with 54% men and 46% women [5]. In a series consisting of 906 jejunal and ileal GISTs, the mean age was 59 years [6].

The presentation of GISTs ranges from asymptomatic to mild abdominal pain and mass (5–50%) and mechanical obstruction (5%) as well as hemorrhage – perforation having rarely been reported (0.8%) – making the diagnosis difficult. Exophytic growth of these tumors has been noted in 18–30% of cases [7]. We present a female case had a history of GI 3 years earlier followed by a diagnosis of jejunal GIST after undefined abdominal pain and no further history of bleeding with an exophytic growth only.

Case Report

A 62-year-old Bangladeshi female had a history of hematemesis and melena 3 years earlier. For that she had been admitted and had needed ICU care for recovery, though upper GI endoscopy had revealed normal results. From then on she had not had any new complaint, but had recently developed occasional abdominal pain and lumpy feelings in the right side of the abdomen, but no history of melena/hematemesis this time. When she was examined for evaluation, a diffuse lump was felt in the right iliac region. A computed tomography (CT) scan of the whole abdomen showed a heterogeneously enhancing, predominantly solid mass measuring about 5.7 × 5 cm in the right iliac region within the mesentery (Fig. 1). After proper counseling, an exploratory laparotomy was carried out in view of small intestinal mass and appendicitis. On midline incision, there was a 6 × 6 cm mass in the jejunum approximately 30 cm from the duodenojejunal flexure. Resection and anastomosis of the tumor was done, and another small tumor was found proximally that was also excised and repaired. Peroperatively the liver was free of any tumor and lesion (Fig. 2). No other intra-abdominal lesion was found. Appendectomy was also done due to its inflamed looked. Histopathology showed a jejunal mass GIST, intermediate risk group of malignancy (Fig. 3). (Gross description: 10-cm resected small intestinal mass containing an about 6-cm solid mass that protruded outward from the serosal surface, no lymph nodes found. Microscopic descriptions: section showing jejunum that contained a mesenchymal neoplasm located in the submucosa, the tumor was made of fibroblastic cells arranged in fascicles and whorls, mitotic figures were <5/50 HPF, all resection margins were free from tumor.) The jejunal nodule showed no granuloma or malignant cell. Immunocytochemistry for CD117/c-Kit showed positive expression (Fig. 4). Due to intermediate risk group as for the position itself (in the jejunum) she was expected to benefited from a tyrosine kinase inhibitor (imatinib) because there was a 24% probability of disease recurrence without treatment. Thus, imatinib was started, and she has been on follow-up for 2 years without showing any recurrence.

Discussion

In the digestive system, from mouth to anus, mesenchymal origin of tumors is quite rare; in general, they are recognized as GISTs. The incidence of GISTs in the alimentary tract is very low (2 in 100,000) and is about 1% of all GI malignancies [1], but jejunal GISTs are extremely rare, accounting for 0.1–3% of all GI tumors [2]. The stomach is the main site of presentation (two-thirds) [3], followed by the small intestine (one-fourth), usually the duodenum [4] and less commonly (<5%) the rectum, esophagus, omentum, and mesentery [3, 8]. As per the literature, jejunal GISTs are the rarest among all types of GISTs [2]. There is a minimal male
Fig. 1. Computed tomography image of the abdomen and pelvis showing an inhomogeneous mass in the right iliac fossa.

Fig. 2. Peroperative specimen.

Fig. 3. Histopathology examination.
predominance with 54% men and 46% women [5], but no association with geographic location or ethnicity could be documented [9]. GISTs are sporadic [3]. Familial forms with autosomal dominant inheritance have also been documented [3, 9]. Over 90% of GISTs occur in adults aged >40 years. The incidence peak of diagnosis is 60–65 years [9], but in a series consisting of 906 jejunal and ileal GISTs, the mean age was 59 years [6].

The presentation of GIST often depends on their size. Most of the time it is asymptomatic to mild abdominal pain and mass (5–50%), mechanical obstruction (5%), as well as hemorrhage and rarely perforation (0.8%) [10, 11], making the diagnosis difficulty. Small GISTs <2 cm are asymptomatic and incidentally detected at laparotomy or endoscopy [3]. The features of larger tumors include vague abdominal discomfort, acute/chronic GI bleeding, intestinal obstruction, or altered bowel habits [3]. Very large GISTs presenting as exophytic palpable masses are likely to be malignant [3]. However, GISTs presenting with perforation and peritonitis are an extremely rare phenomenon [12]. In our case, only GI bleeding and melena were the initial symptoms.

The most common clinical manifestation for GISTs is occult GI bleeding from mucosal ulceration. Five percent of GI hemorrhage is obscure in nature, and GISTs have been described as one of the causes [13]. There are few factors that may contribute to hemorrhage of jejunal GISTs. First, location at the small bowel is associated with the highest incidence of bleeding. Of all small bowel GISTs, 64% present with bleeding, whereas gastric, colonic, and rectal GISTs have been associated with a <50% incidence of bleeding [14]. Second, although extraluminal in origin, GISTs may ulcerate through the overlying mucosa, causing intraluminal bleeding [14]. Third, stromal collagen is minimal in most GISTs, but delicate, thin-walled vessels may be prominent, making stromal hemorrhage a common feature of these tumors [14].

The diagnosis of small intestine GISTs is always very difficult with barium swallow/enema, upper GI endoscopy/colonoscopy, or even percutaneous/endoscopic ultrasound. Capsule endoscopy is one way to look at the small intestine as the capsule travels through the intestine and takes thousands of pictures. CT scanning with intravenous and oral contrast material makes the diagnosis and staging of GISTs likely [15]. Ghanem et al. [16] described the CT characteristics of GISTs on the basis of size, as follows: Small (<5 cm): sharply demarcated, homogeneous masses, mainly exhibiting intraluminal growth patterns. Intermediate
(5–10 cm): irregular shape, heterogeneous density, an intraluminal and extraluminal growth pattern, and signs of biological aggression, sometimes including adjacent organ infiltration. Large (>10 cm): irregular margins, heterogeneous densities, locally aggressive behavior, and distant and peritoneal metastases. In our case, the CT scan finding was a heterogeneously enhancing mass, predominantly solid, measuring about 5.7 × 5 cm, in the right iliac region within the mesentry.

However, CT enterography has some benefit over conventional CT scan to detect small bowel pathologies, as it provides good luminal distention provided by negative oral contrast agents and good bowel wall visualization, for suspected inflammatory bowel disease, but also for detecting occult GI tract bleeding, small bowel neoplasms, and mesenteric ischemia [17]. MRI can be an especially helpful adjunct to CT in the evaluation of large tumors that have necrotic and hemorrhagic components. Solid tumor portions show low intensity on T1 images and high intensity on T2 images, with enhancement of the mass when intravenous gadolinium is given. The signal intensity of hemorrhagic components of the tumor can vary from high to low, depending on the age of the hemorrhage [18].

Nowadays, GISTs may be defined morphologically as spindle cells, epithelioid cells, or occasional pleomorphic mesenchymal tumors originating from interstitial cells of Cajal or related stem cells expressing CD117/c-Kit protein in 95% of the cases, regardless of site of origin, histological appearance, and biological behavior [19]. The definite diagnosis therefore relies on a combination of both immunohistochemical assay and morphological histology [20]. The current recommendations for assessing the risk of compression rely on three parameters: tumor size, location, and mitotic index. In the presented case, a 6-cm maximal diameter jejunal GIST with five mitoses/HPF (5 mm) indicates an intermediate probability of metastases and a recurrence risk of 24% [21].

Surgical resection is the primary treatment for jejunal GISTs. Evidence does not indicate an optimal resection margin size, but a negative margin is vital to prevent local recurrence. Lymph nodes are rarely involved and as such their dissection is not typically indicated. Complete resection of an intermediate-risk GIST, such as in the present case, results in 95% 5-year survival.

Small intestine GISTs are more destructive than those of the stomach, with approximately 40–50% of small bowel GISTs showing malignant behavior compared with 20–25% of gastric GISTs [22]. Complete en bloc resection with clear surgical margins is the primary treatment for localized GISTs [22].

As per National Cancer Institute recommendations for GISTs, patients with a tumor size >10 cm, which is labeled as histopathologically high-risk category, benefited more from imatinib than those with smaller tumors. ASCO-2010 and the trial by Nilsson et al. [7] indicate that 1 year of adjuvant therapy with imatinib 400 mg/day dramatically improves recurrence-free survival. Imatinib as such is recommended in metastatic, residual, or recurrent cases of GISTs or tumors which are not removable surgically; however, recent recommendations suggest the use of imatinib mesylate after radical surgery in high-risk cases because it has shown a 14% absolute decrease in the recurrence rate (97% of the patients receiving imatinib were free of recurrence compared to 83% in the placebo group) [23].

The prognostic factors of GISTs include age at presentation, anatomic location, size (most important), histomorphology, immunohistochemistry, and molecular genetics [9, 24–29]. Positron emission tomography with 18F-fluoro-2-deoxy-D-glucose is a very useful tool for the postoperative follow-up of patients receiving imatinib [9, 24, 28, 29].
Conclusion

The role of this case report is to make readers aware of the diagnostic difficulty in a low socioeconomic conditional country like Bangladesh, and to keep in mind that any undiagnosed GI bleeding should be considered as a case of GIST and should be closely monitored. Further symptoms with available investigations and physical examination may lead to confirmation of the diagnosis, although most of the time diagnostic laparotomy is the only option to prove the diagnosis. Early detection and availability of treatment may improve overall survival as well as disease-free survival in most cases.

Statement of Ethics

The authors have no ethical conflicts to disclose.

Disclosure Statement

The authors have no conflicts of interest to declare. There was no funding source.

Author Contributions

F.A. Begum: writing and overall patient diagnosis, management, and specific oncological treatment. M.A. Rahman: literature search and helping the writing of the paper. H. Rabbi: successful operation. G. Mostofa: histopathological confirmation. Q. Chowdhury: patient management and help with treatment.

References

1. Joensuu H. Gastrointestinal stromal tumor (GIST). Ann Oncol. 2006 Sep;17 Suppl 10:x280–6.
2. Kramer K, Siech M, Sträter J, Aschoff AJ, Henne-Bruns D. [GI hemorrhage with fulminant shock induced by jejunal gastrointestinal stromal tumor (GIST) coincident with duodenal neuroendocrine carcinoma (NET) + neurofibromatosis (NF) – case report and review of the literature]. Z Gastroenterol. 2005 Mar;43(3):281–8.
3. Miettinen M, Sobin LH, Lasota J. Gastrointestinal stromal tumors of the stomach: a clinicopathologic, immunohistochemical, and molecular genetic study of 1765 cases with long-term follow-up. Am J Surg Pathol. 2005 Jan;29(1):52–68.
4. Goldblum JR. Gastrointestinal stromal tumors. A review of characteristics morphologic, immunohistochemical, and molecular genetic features. Am J Clin Pathol. 2002 Jun;117 Suppl 549–61.
5. Tran T, Davila JA, El-Serag HB. The epidemiology of malignant gastrointestinal stromal tumors: an analysis of 1,458 cases from 1992 to 2000. Am J Gastroenterol. 2005 Jan;100(1):162–8.
6. Miettinen M, Makhlof 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. Am J Surg Pathol. 2006 Apr;30(4):477–89.
7. Nilsson B, Sjölund K, Kindblom LG, Meis-Kindblom JM, Bümming P, Nilsson O, et al. Adjuvant imatinib treatment improves recurrence-free survival in patients with high-risk gastrointestinal stromal tumours (GIST). Br J Cancer. 2007 Jun;96(11):1656–8.
8. Sam JJ, Mustard R, Kandel G, Gardiner G, Ghaffar H, Kirpalani A, et al. Colonoscopy leads to a diagnosis of a jejunal gastrointestinal stromal tumour (GIST). Gastroenterology Res. 2011 Dec;4(6):277–82.
9. Sornmayura P. Gastrointestinal stromal tumors (GISTs): a pathology view point. J Med Assoc Thai. 2009 Jan;92(1):124–35.
10. Efremidou EI, Liratzopoulos N, Papageorgiou MS, Romanidis K. Perforated GIST of the small intestine as a rare cause of acute abdomen: surgical treatment and adjuvant therapy. Case report. J Gastrointestin Liver Dis. 2006 Sep;15(3):297–9.
11. Oida Y, Motojuku M, Morikawa G, Mukai M, Shimizu K, Imaizumi T, et al. Laparoscopic-assisted resection of gastrointestinal stromal tumor in small intestine. Hepatogastroenterology. 2008 Jan-Feb;55(81):146–9.
Jagtap SV, Nikumbh DB, Kshirsagar AY, Bohra A, Khatib W. Malignant gastrointestinal stromal tumor of the sigmoid colon with perforation and peritonitis – an unusual presentation. *Int J Health Sci Res*. 2012;2(3):104–9.

Spiller RC, Parkins RA. Recurrent gastrointestinal bleeding of obscure origin: report of 17 cases and a guide to logical management. *Br J Surg*. 1983 Aug;70(8):489–93.

Daldoul S, Moussi A, Trili W, Baraket RB, Zaouche A. Jejunal GIST causing acute massive gastrointestinal bleeding: role of multidetector row helical CT in the preoperative diagnosis and management. *Arab J Gastroenterol*. 2012 Sep;13(3):153–7.

Guideline ESMO/European Sarcoma Network Working Group. Gastrointestinal stromal tumours: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2014 Sep;25 Suppl 3:iii21–6.

Ghanem N, Altehoefer C, Furtwängler A, Winterer J, Schäfer O, Springer O, et al. Computed tomography in gastrointestinal stromal tumors. *Eur Radiol*. 2003 Jul;13(7):1669–78.

Elsevies KM, Al-Hawary MM, Jagdish J, Ganesh HS, Platt JF. CT enterography: principles, trends, and interpretation of findings. *Radiographics*. 2010 Nov;30(7):1955–70.

Gastrointestinal Stromal Tumors (GISTs) Workup. https://emedicine.medscape.com/article/278845-workup#e4.

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 May;33(5):459–65.

Kingham TP, DeMatteo RP. Multidisciplinary treatment of gastrointestinal stromal tumors. *Surg Clin North Am*. 2009 Feb;89(1):217–33.

Roy SD, Khan D, De KK, De U. Spontaneous perforation of jejunal gastrointestinal stromal tumour (GIST). Case report and review of literature. *World J Emerg Surg*. 2012 Nov;7(1):37.

de Silva CM, Reid R. Gastrointestinal stromal tumors (GIST): c-kit mutations, CD117 expression, differential diagnosis and targeted cancer therapy with imatinib. *Pathol Oncol Res*. 2003;9(1):13–9.

DeMatteo R, Owzar K, Maki R, et al. Adjuvant imatinib mesylate increases recurrence free survival (RFS) in patients with completely resected localized primary gastrointestinal stromal tumor (GIST). North American Intergroup phase III trial ACOSOG Z9001. *J Clin Oncol*. 2007;25:A10079.

Steigen SE, Bjerkehagen B, Haugland HK, Nordrum IS, Løberg EM, Isaksen V, et al. Diagnostic and prognostic markers for gastrointestinal stromal tumors in Norway. *Mod Pathol*. 2008 Jan;21(1):46–53.

Wilson SL, Wheeler WE. Giant leiomyoma of the small intestine with free perforation into the peritoneal cavity. *South Med J*. 1992 Jun;85(6):667–8.

Shah SN. Malignant gastrointestinal stromal tumor of intestine: a case report. *Indian J Pathol Microbiol*. 2007 Apr;50(2):357–9.

Huang CC, Yang CY, Lai IR, Chen CN, Lee PH, Lin MT. Gastrointestinal stromal tumor of the small intestine: a clinicopathologic study of 70 cases in the postimatinib era. *World J Surg*. 2009 Apr;33(4):828–34.

Kingham TP, DeMatteo RP. Multidisciplinary treatment of gastrointestinal stromal tumors. *Surg Clin North Am*. 2009 Feb;89(1):217–33.

Annaberdyev S, Gibbons J, Hardacre JM. Dramatic response of a gastrointestinal stromal tumor to neoadjuvant imatinib therapy. *World J Surg Oncol*. 2009 Mar;7(1):30.