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Laparoscopic Small Bowel Resection And Anastmosis For Small Proximal Jejunal Gastrointestinal Stromal Tumor Presented With Acute Massive Lower Gastrointestinal Bleeding: Case report and Literature review

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Case report

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Abstract

Background Gastrointestinal stromal tumors (GISTs) is the most common primary nonepithelial neoplasms of the gastointestinal tract, mostly expressing the KIT protein determined by immunohistochemical staining for the CD117 antigen. Jejunal GISTs represent approximately 10% of all GISTs. Abdominal discomfort is the usual presentation. Jejunal GISTs may present with complications such as intestinal obstruction or hemorrhage. Gastrointestinal bleeding occurs due to pressure necrosis and ulceration of overlying mucosa, and patients who develop significant bleeding may suffer from fatigue and malaise. Small-bowel GISTs are classified based on size, and several guidelines have recommended conservative treatment for small jejunal GISTs (<2 cm).

Case presentation In this report, we describe a 35-year-old male, with a jejunal GIST, who presented with an unusual massive lower GI bleeding. After resuscitation extensive work up, he was taken finally for a diagnostic laparoscopy and resection of the mass.Conclusion Small intestinal GISTs are rare and unusual to present with massive lower GI bleeding.

Introduction

A gastrointestinal stromal tumor (GIST) is a rare mesenchymal tumors of the gastrointestinal tract that arising from any site of the alimentary tract. The commonst anatomical site is the stomach, but it can develop anywhere in the digestive tract. The anatomical distribution of GISTs is two thirds occur in the stomach and one fourth develops in the small bowel mainly the duodenum. GISTs are uncommon mesenchymal neoplasms of the alimentary tract [1]. The overall incidence of GIST is very low (2 in 100,000), while jejunal GIST account for 0.1–3 % of all digestive tract tumors which is extremely rare [2]. Based on tumor size, small-intestinal GISTs smaller than 2 cm can be considered as small GISTs [3]. The most common presentation of jejunal GISTs are vague abdominal pain and discomfort. Overlying mucosa pressure necrosis and ulceration may cause gastrointestinal hemorrhage. We report a case of a very small jejunal GIST presenting with massive lower gastrointestinal bleeding.

Case Report

A 35-year-old male, presented to the emergency department with massive lower GI bleeding. He had no associated symptoms and he was not on any medications. In regards to his medical history, he denied any major diseases or a risk factor for bleeding

On examination, he was oriented, fully conscious but looked pale. His pulse rate was 130 beat per minute, blood pressure of 130/80. Abdominal examination was unremarkable. Per rectal examination showed hematochizia.

Nasogastric tube was inserted immediately and showed clear output. Blood tests showed hemoglobin level of 8 g/dL, hematocrit of 25, and normal platelet level. Kidney and liver function tests were also normal.

Transfusion of 3 units of packed red blood cells (PRBCs) was initiated. Infusion of proton pump inhibitors at a rate of 80 ml/hr was also given.

After resuscitation, patient was shifted to the endoscopy suite for upper and lower endoscopy.

While upper gastrointestinal endoscopy was normal to the second part of duodenum, lower gastrointestinal endoscopy showed that the colon filled with blood and also there is blood coming from the distal ileum through ileocecal valve (**Figure 1**).

After that, our patient underwent a CT abdomen with IV contrast which showed a 2 x 2 cm mass in proximal jejunum with extravasation of contrast at that site (**Figure 2**). Therefore, SMA angiography with embolization of the bleeder was attempted. This study confirmed the results of the CT, but embolization was not successful (**Figure 3**).

The decision was made to shift the patient to the operation room for emergency surgery after obtaining an informed consent. Laparoscopic exploration of the abdomen revealed small bowel filled with blood **(Figure 4)**and the previously mentioned mass on the antimesenteric border of the proximal jejunum (**Figure 5**) . It was resected and primarily anastomosed (**Figure 6**).

CT abdomen was repeated 48 hour after the surgery and showed an intact anastomosis and no evidence of leak. Liquid diet allowed and advanced to full as tolerated. Patient had a smooth postoperative period without any complications.

Hisopathologic analysis of the specimen showed well defined submucosal spindle cell tumor extending beyond musculosa and serosa. The tumor formed of of spindle cells arranged in fascicles separated by fibrous septa. The cells have eosinophilic cytoplasm with oval spindle shape nuclei. Immunohistochemistry was positive for CD117**(Figure 7).**

He was finally discharged home a week after the surgery with a follow up in outpatient clinic.As the tumor was classified as a low risk for recurrence based on the histopathological findings, adjuvant therapy in term of Tyrosine Kinase Inhibitors was not initiated.

Figure (1): Colon filled with blood.

Figure (2): CT abdomen with IV contrast showed proximal jejuna mass with extravasation (red arrow).

Figure (3): SMA angiography showed extravasations (yellow arrow).

Figure (4): Bowel filled with blood (red arrow).

Figure (5): GIST in proximal Jejunum (green arrow).

Figure (6): laparoscopic small bowel resection anastmosis.

Figure (7): Spindle cell GIST, (A) hematoxylin and eosin stain (H&E), (B) KIT expression by immunohistochemistry,low magnification, (C) KIT expression, high magnification.

Mesenchymal or stromal tumors of the gastrointestinal tract divided into two major groups. The first one is the gastrointestinal stromal tumors (GISTs) which is the most common, the second one is less commom and formed of a variety of neoplasms that are similar to that originate from soft tissue of the body and include leiomyomas, lipomas, desmoid tumors, peripheral nerve sheath tumors, leiomyosarcomas and liposarcomas[4-8].

Gastrointestinal stromal tumors are most commonly arise from the stomach and proximal part of the small bowel, it also can developed in any part of the gastrointestinal tract and occasionally in extragstrointesinal sites like omentum and retroperitoneum.GISTs characterized by expression of KIT protein and mutations in KIT gene and platelet-derived growth factor receptor alpha (*PDGFRA)* gene [8].

GISTs tumors are the most common submucosal non epithelial neoplasm of the gastrointestinal tract, it account for less than 1% of primary intestinal cancers [5, 9]. The prevalence of GISTs tumors is the third after gastrointestinal adenocarcinoma and lymphoma [10]. Between 2001 and 2011 Surveillance, Epidemiology and End Results (SEER) analysis detected 6142 cases of histologically confirmed GIST with incidence approximately of 0.68 per 100,000 [11]. Prospective study from 2005 to 2007 in French Rhone Alps region showed incidence of GISTs is 11.2 per million per year. I united states about 5000 newly diagnosed case per year [12].

GIST occur most commonly in middle aged and older people and rare before the age of 40. Analysis of the SEER registered data mentioned before; the age at the time of diagnosis was 66 to 69 years (mean age 64 years) in 3 European population-based studies [12-14].

The vast majority of GIST are sporadic. Approximately 5% are syndromic including neurofibromatosis type 1 (NF1), primary familial GIST syndrome, and Carney-Stratakis syndrome, all are familial autosomal dominant syndromes. Sporadic GIST cannot differentiated phenotypically, histologically and genetically from familial GIST [15-16].

Intially GISTs were considered to originate from smooth muscle of the gastrointestinal tract according to histopathological features. However the immunophenotypic features of GISTs totally different from that of leiomyosarcoma and leiomyoma that derived from other tissues containing smooth muscles like uterus. In 1990, GISTs appeared that they are different from other gastrointestinal mesenchymal tumors. GISTs were found to be positive for CD34 in up to two-third of patients [17-18].

The cellular origin of GISTs is the interstitial cells of Cajal (ICCs) which are the pacemakers of the gastrointestinal tract that are responsible for regulation of peristalsis. They act as connection between the autonomic innervations and smooth muscles of the intestinal wall. The interstial cells of Cajal have ultrastructure and immunophenotypic characteristics of both smooth muscles and neuronal differentiation. The association between the ICCs and GISTs has been suggested based on both of them express KIT protein and also CD34 expressed in two-third of GISTs cases. It is presumed that GISTs arise from CD34-positive ICC cells and differentiate into the pacemaker cell phenotype [17, 19-22].

To confirm that the GISTs originate from ICCs is the resected tumors are associated with diffuse ICC hyperplasia within the intestinal wall in many families with GIST.These lesions are supposed to act as precursor lesions to GIST in such patients. Sporadic tumors may also harbor diffuse ICC hyperplasia, in such cases it is mandatory to differentiate between the sporadic and syndromic GIST (hereditary GIST syndromes) [23-30].

The conflict of hypothesis of GISTs derived from ICCs is extra-gastrointestinal GISTs (EGISTs) which are similar phenotypically to GISTs. It is suggested that these tumors originate from ICCs that are incidentally scattered during embryogenesis [6, 21, 25, 27].

Most of GISTs are due to gain –of – function mutation of c-*kit* proto-oncogene especially exon 11. The location of c-kit proto-oncogene is 4q11-12 and encodes transmembrane tyrosine kinase KIT. Most of c-kit mutations are frame type mutation which allows preservation of activation and expression of c-kit [32].

Normally KIT activation started by binding of stem cell factor (steel factor or mast cell growth factor) to extracellular domain of c-KIT result in homodimerization of the inactive monomers of c-KIT. Homodimerization of monomers is followed by auto-phosphorylation of intracellular residues of tyrosine kinase result in exposure of of intracellular signal transduction molecules binding sites. This followed by activation of several pathways like MAP kinase, RAS and others which result in transduction of signals inside the nucleus and lead to mitogenic activity and protein transcription [32-33].

In most of GISTs, KIT is activated and phosphorylated without stem cell factor (ligand- independent activation) result in increased transduction of signals to the nucleus support survival of cells and enhance cell replication over apoptosis and dormancy leading to oncogenesis[33].

Approximately 95% of GISTs are positive for KIT while 5% are negative. In those with KIT- negative GISTs, PDGFRA are mutated. Discrimination between KIT-negative GISTs and other mesenchymal tumors of gastrointestinal tract can be done using immunostainig of PDGFRA. There are small proportion of patients with GISTs lacking KIT/PDGFRA have mutation in BRAF, DOG-1 and protein kinase C theta (PKCtheta) gene. Initial studies reported that GISTs with BRAF mutations have tendency for small intestine without high risk of malignancy [34-35].

Stomach is the most common site of GISTs account for 50-70% lop (70% in cardia ,15% in cardia and fundus and 15% in antrum) followed by small bowel (20-30 of GISTs arise in jejunum and ileum). Rare sites include colon and rectum (5-15%) and esophagus (less than 5%). Primary extra- gastrointestinal GISTs has been reported in omentum, mesentery and pancreas but extremely [35-36].

GISTs are classified histopathologically into three categories 1-spindle cell type (70%), 2-epitheliod type (20%), and 3-mixed type (10%). Spindle cell type is formed of uniform cells with eosinophilic cytoplasm arranged in whorls or fascicles as in our case. Epithelioid type has cells with either clear or esinophilic cytoplasm **(Figure 8)** and is mostly KIT negative but has PDGFRA gene mutations and occurs commonly in stomach. Mixed type GISTs harbor areas of transition between epithelioid and spindle cell types **(Figure 9)** [7, 17, 19].

Figure (8): Epithelioid GIST, hematoxylin and eosin stain (H&E).

Figure (9): Mixed GIST, epithelioid component (red arrow) and spindle component (yellow arrow).

Some GISTs are diagnosed accidentally either during endoscopy as subepithelial mass or on cross sectional imaging for other reasons. GISTs may be associated with non specific symptoms as bloating and early satiety unless they complicated by ulceration, bleeding or grow large to cause pain and obstruction. In general the clinical manifestation of GISTs is: 1- gastrointestinal bleeding either overt or occult (50% gastric and 20% small bowel), 2-abdominal pain (8-17%), 3-accidental finding (13-18%), 4-acute abdomen (2-14%), 5- abdominal mass (5%) [1, 37].

GISTs are rarely associated with paraneoplastic syndromes however there are paraneoplastic syndromes reported in few patients like hypoglycemia (non-islet cell tumor hypoglycemia) and hypothyroidism (consumptive hypothyroidism) [38].

Metastasis to other sites in patients with GISTs occurs late in the course of the disease in most patients and commonly involves the liver and peritoneum. Lymph node metastasis is extremely rare, approximately 0-8% of patients with GISTs develop lymph node metastasis. However in pediatric patients with GISTs the lymph node and distatnt metastasis are common and present at time of diagnosis [39].

Patients with multifocal GISTs are considered as metastatic (advanced) GITSs, inspite of some patients (especially those with rare hereditary GISTs syndromes) are affected by multiple lesions [40].

Contrast-enhanced computed tomography (CECT) with oral and intravenous contrast is the imaging of choice to evaluate any abdominal mass. It provide information regarding size, extent, location, presence of multiple tumors, invasion into surrounding structures and presence or absence of distant metastasis which affect mainly peritoneum and liver [41-42].

GISTs are characterized byGhanem and colleagues based on the size as follow [43]:

- Small GIST (less than 5cm): well demarcated homogenous mass with intraluminal growth pattern.
- Intermediate GIST (5-10cm): irregular heterogeneous mass with both extraluminal and intraluminal growth pattern and may have signs of aggressive biological behavior as infiltration of adjacent organs.
- Large GIST (more than 10cm): irregular heterogeneous mass with signs of aggressive biologic behavior such as local infiltration, distant and peritoneal metastasis.

Magnetic resonance imaging (MRI) can be used in adjunction with CT for evaluation of large tumors that have hemorrhagic and necrotic component. Solid parts of the mass have low signal intensity on T1 and high signal intensity on T2 images with enhancement of tumor after administration of intravenous gadolinium. MRI is also helpful for evaluation of tumors at certain sites such as rectum to evaluate anatomic extent of tumors including sphincter involvement and also helpful for evaluation of liver for metastasis. The advantages of MRI are lack radiation exposure and are preferred in patients who cannot take intravenous contrast [42].

Endoscopy may be helpful to characterize the lesion if gastric mass identified on image. GISTs and leiomyomas appear as submucosal mass with bulging inside gastric lumen and intact overlying mucosa. Central ulceration of the overlying mucosa may be seen. Endoscopy alone cannot differentiate between extramural and intramural mass. So, endoscopic ultrasound (EUS) has major advantages including identification of layer of origin of tumor and enable tissue biopsies for histopathological studies including immunohistochemistry. GISTs appear as hypoechoic, homogenous with well-defined border on EUS, although they may have ulceration and irregular margins.Most of GISTs arise from the muscularispropria (4^{th} layer of the gastrointestinal tract) while small tumors may arise from the muscularis mucosa (2nd layer of the gastrointestinal tract). Occasionally the tumors appear heterogenous because of liqufactive necrosis, connective tissue, and connective tissue, and hyaline and cystic degeneration of the tumors [44].

The rule of Positron emission tomography (PET) scanning using fluorodeoxyglucose (FDG-PET) in GISTs is early detection of response to tyrosine kinase inhibitors (TKIs) like imatinib which may be necessary when treatment given as neoadjuvant therapy. Response to imatinib appear as marked reduction of glycolytic metabolism on FDG-PET which can be seen 24 hours after imatinib therapy is started. Also FDG-PET can be helpful in detection of tumor of unknown primary site or resolving equivocation from CT (eg, when there are ambiguities between CT and clinical findings). The sensitivity of FDG-PET for GISTs (including metastatic disease) is 86 to 100 percent [45, 46, 47].

Preoperative biopsy is not indicated in a respectable tumor in which there is a strong suspicion for GIST and the patient is operable. The indications of biopsy are 1- to confirm diagnosis if metastatic disease is suspected, 2- if preoperative imatinib is indicated before attempted resection in a patient with a large locally advanced tumor with high suspicion for GIST. If preoperative biopsy is indicated EUS guided biopsy is better than image-guided percutanous biopsy because of the risk of rupture of tumor capsule and peritoneal implantation of tumor cells associated with percutanous biopsy, although there is strong

evidence in patients receiving imatinib that patients undergoing percutaneous biopsy have inferior outcomes in comparison to patients who do not. The combination of histopathological analysis, immunohistochemical analysis for KIT protein expression, and polymerase chain reaction(PCR) for *KIT* mutations may help the diagnosis of most of submucosal lesions by EUS-guided fine-needle aspiration (EUS-FNA). In one study including 65 patients underwent EUS-FNA for an upper gastrointestinal tract submucosal tumor, the sensitivity and specificity for diagnosis of GIST was 82 and 100 percent, respectively [48-49].

Inspite of the proven success of imatinib therapy and newer tyrosine kinase inhibitors, surgical resection is the main line of treatment for localized GIST and exhibit the only chance for cure from GIST. The main principle in operative resection of GIST is resection with negative microscopic margins. Resection with wide margin (eg, 2 cm margin) has not been approved to improve outcomes and expert consensus is that assertive adherence to resection with wide margin is not essential or recommended [41, 53-58].

Local resection for small GISTs is adequate, if it is technically feasible and does not affect a complete resection. Segmental resection is recommended for small bowel GIST and wedge resection may be adequate for gastric tumors in certain case. Enucleation is contraindicated for small tumors because prediction of malignant GISTs preoperatively is difficult even are the tumor looks benign [59].

En bloc resection of adjacent organs as colon, liver, or spleen may be adequate for locally advanced tumors. lymphadenectomy is not recommended because lymph node metastasis is extremely rare [60].

Type of resection (wedge resection versus gastrectomy) does not affect survival or recurrence rate provided that complete resection (R0) done. Every effort should be done to avoid tumor rupture because rupture of tumor is associated with bad prognosis due to peritoneal seeding [59, 60].

Palliative resection may be considered in patients with disseminated disease, because long-term survival has been documented in certain cases. Also resection is considered in cases with recurrent disease that presents with solitary lesion in the liver or peritoneal cavity. Published data of hepatic resection for liver metastasis from gastric and other GISTs suggest better survival in selected cases [60, 61].

Because of the ability of imatinib therapy to make initially inoperable GISTs resectable, there is a role for cytoreductive surgery (R0 or R1 resection) in patients presented with recurrent metastatic disease limited to the abdomen. Patients should recieve at least 6 months of imatinib therapy or another TKIs and have had either partially responsive or stable tumor during this period. 40% of these patients needs hepatic resection and 60% require multivisceral resection including omentectomy, peritonectomyand/or intestinal resection. Even after aggressive resection, microscopically positive margins (R1 resections) are the rule, R0 resections are rare and approximately 5% of cases still have bulky disease as a remnant [60, 61, 62].

Up to 70% of patients with stable or partially responsive disease after imatinib therapy who undergo R0/R1 resection have a progression-free survival (PFS) as long as 4 years [62].

Given that adequate surgical resection for small malignant GISTs can be accomplished by wedge resection, minimally invasive surgical approaches can be considered in certain cases, such as those in suitable locations (eg, the greater curvature of the stomach or anterior gastric wall) [63].

Laparoscopic resection is used for treatment of GISTs. Chen et al reported that laparoscopic resection was technically feasible for GISTs not more than 5 cm situated at the stomach and small intestine. Advantages of laparoscopic surgical resection included faster returning of a normal diet, shorter hospital stays after surgery, and less use of analgesia. Short-term oncological results were similar to open surgery [64].

Several published studies of laparoscopic resection of gastric GISTs have elucidated the feasibility and safety of this approach. In a retrospective study included 666 patients who underwent surgical resection for GISTof the stomach less than 20cm, Piessen et al reported that laparoscopic resection of gastric GISTs had significant lower overall, surgical, and medical morbidity, and better 5-year recurrence-free survival (RFS). Furthermore, subgroup analysis of patients with tumors greater than 5 cm showed that laparoscopic and open approaches had comparable hospital morbidity and 5-year RFS [65-71].

Estimation of the risk of recurrence following surgical resection of GIST is of greater significance in selection of patients who could benefit from adjuvant imatinib. There are a lot of risk stratification models such as the original National Institutes of Health (NIH) consensus model , has beem used to detect prognosis in surgically resected GIST (Table 1) [50].

In the series including 289 patients applied this model the cumulative disease specific five-year survival rates for risk level I through IV risk were 100%, 96%, 67%, and 25%, respectively. The prognostic significance of mitotic rate, tumor size, and anatomical location was confirmed analysis of ACOSOG Z9001 trial [51].

NIH risk stratification model do not take into account the anatomical location of the primary GIST tumor.Overall, tumors originating from the small intestine, colon, rectum, or mesentery have less favorable outcomes in comparison to those arising from the stomach [1, 37, 52].

Other risk stratification models have taken into account anatomical site of GIST origin, for example the Armed Forces Institute of Pathology (AFIP), use a tumor, node, and metastasis (TNM) staging system for risk stratification. Although the T and N installation are similar for all disease sites, there are different stage groupings for gastric/omental and small bowel/esophageal/colorectal/mesenteric and peritoneal primary tumors as in (Table2) [52, 72, 73].

Table (1): Modified NIH consensus criteria for risk stratification of GISTs

Risk group	Size, cm	Mitotic rate, per 50 HPF
Level I	≤5	<5
Level II	<5	6-10
	5-10	<5
Level III	≤5	>10
	5-10	6-10
	>10	<5
Level IV	>5	>10

Table (2): Incidence of progression-free survival for GISTs of stomach, small bowel, and rectum based on mitotic rate and tumor size

Tumor size (cm)	Mitotic rate (HPFs)	Percent of patients progression-free survival during long-term follow-up according to Primary site			
		Gastric	Jejunum/ileum	Duodenum	Rectum
≤2	≤5/50	100	**100**	**100**	**100**
2 to 5	≤5/50	**98.1**	**95.7**	**91.7**	**91.5**
5 to 10	≤5/50	96.4	76	**66[α]**	**43[α]**
>10	≤5/50	88	48	**66[α]**	**43[α]**
≤2	>5/50	**100[Δ]**	**50[Δ]**	**-**	**46**
2 to 5	>5/50	**84**	**27**	**50**	**48**
5 to 10	>5/50	**45**	**15**	**14[α]**	**29[α]**
10	>5/50	**14**	**10**	**14[α]**	**29[α]**

HPFs: high power fields, [α] Data are combined for tumors >5 cm, [Δ] Small number of cases.

Although tumor rupture and incomplete surgical resection are not included in TNM staging system, they are independent predictors that negatively affect prognosis.A modification of the NIH risk stratification model has been suggested that mingle both site and tumor rupture as prognostic factors [74, 75, 76].

As alternative to risk stratification models, others use GIST tumor nomogram for detection of the rates of disease recurrence after complete surgical resection. Different nomograms are available [77, 78, 79].

Data from the Scandinavian Sarcoma Group (SSG) XVIII trial recommend adjuvant therapy with a tyrosine kinase inhibitors TKI (imatinib 400 mg daily) for patients who underwent complete resection of primary high risk GIST for a minimum of three years [79]. It is not known whether treatment with a TKI should be given for more than three years. Rates of recurrence of GIST is high within 6 to 12 months of discontinuation of adjuvant imatinib for up to three years, and it is likely that imatinib is preserving tumor dormancy rather than eradication of microdeposits. Patients with high-risk tumors may select to remain on a well-tolerated medication instead of increased rate of recurrence following discontinuation of the drug [81, 82].

The benefits of adjuvant imatinib therapy are illustrated in the following phase III trials:

1. ACOSOG Z9001 showed that adjuvant imatinib therapy significantly increase recurrence free survival (RFS) 98% vs. 83% at 1 year; overall hazard ratio 0.35; one-sided p<0.0001) but overall survival was similar in comparison to placebo (99.2% vs. 99.7% at 1 year; hazard ratio 0.66; p=0.47) . the conclusion of this tria;l was that adjuvant imatinib is effective, safe and prolong RFS after surgery for primary GIST in comparison to placebo treatment while OS was similar in both groups [10, 83].
2. EORTC 62024 showed that adjuvant imatinib associated with significant increase in 5-year imatinib failure-free survival (IFFS) (87% versus 84% in the control group, HR 0.79, 98.5% CI 0.50-1.25), 3-year RFS (84% versus 66%) and overall survival (100% versus 99%). Even among high risk GIST patients based on the 2002 NIH classification the adjuvant imatinib significantly increase IFFS (5-year IFFS 79% versus 73%, p = 0.087) but when the risk stratified based on modified NIH risk stratification criteria there is no statistically significant difference in IFFS between treated and control group [84].
3. SSG XVIII trial , The Scandinavian Sarcoma Group (SSG) XVIII trial compared 36 versus 12 months of adjuvant imatinib therapy for 36 versus 12 months (400 mg daily) in 400 high- risk GIST patients. High-risk patients was determined based onthe modified consensus criteria as having one of the following: tumor size more than10 cm, mitotic count more than 10 per 50 high-power fields (HPF), tumor size larger than 5 cm with mitotic rate more than 5/HPF, or rupture of tumor. Approximately 50% of the patients enrolled in trial had primary gastric tumors. After a median follow-up period of 54 months, treatment for long time was associated with a significant improvement in RFS, (5-year RFS 66% versus 48%, HR 0.46, 95% CI 0.32-0.65) and overall survival (92% versus 82 %, HR 0.45, 85% CI 0.22-0.89). With a longer median follow-up of 90 months; patients received three years of adjuvant imatinib continued to have significantly higher RFS (71% versus 52%) and overall survival (92% versus 85%) [19, 80, 85].

Many centers perform genotype all patients with GIST who are candidates for adjuvant imatinib routinely. Adjuvant imatinib therapy is contraindicated in patients with neurofibromatosis (NF)-associated GIST, SDH-deficient GIST, and *PDGFRA* D842V GIST. For patients whose GISTs harbor a *KIT* exon 9 mutations,

high dose of imatinib(800 mg rather than 400 mg daily) is advisable, if tolerated, inspite of there are no data on which these recommendations can be based either for or against this practice [86].

For patients harboring tumors with a *KIT* or *PDGFRA* mutation other than D842V, neoadjuvantimatinib indicated for patients with locally advanced unresectable tumors or borderline resectable tumors, for potentially resectablepGISTs, if reduction in the size of the tumor would result in significant reduction in surgical morbidity and for most patients with GISTof the rectum, unless there is small tumor and sphincter preservation is feasible upfront. If possible, patients with these criteria should be enrolled in a clinical trial [87].

The dose of neoadjuvantimatinib is 400 mg daily. There are some institutions, perform tumor genotyping routinely for all patients before neoadjuvantimatinib. If an exon 9 mutation is detected in a rare patient candidate foneoadjuvantimatinib, the option of a high daily dose (800 mg per day) should be discussed with patients, inspite of there are no data on which these recommendations can be based either for or against this practice. Most of these patients will have primary small intestinal tumor and better referred for initial surgical resection instead of neoadjuvant therapy with imatinib[86].

Patients harboring *PDGFRA* D842V mutated tumor or without *KIT* or *PDGFRA* mutations (wild-type tumors), neoadjuvant imatinib is not recommended because these tumors are insensitive to imatinibtherapy, instead, surgery should be proceeded directly. If genotyping is not available, checking for an early response to imatinib therapy is advisable using computed tomography (CT), positron emission tomography (PET), or contrast-enhanced ultrasound (CEUS) [88].

The ideal duration of TKIs as a neoadjuvant therapy is not well known. There are several factors, the duration of neadjuvantimatinib based on such as anatomical location and extent of tumor, drug tolerance, urgency of surgical resection and the results of frequent radiographic evaluation. So the decision as for how long to give imatinib and when to resect (either at first resectability or after maximal response) must be individualized. Generally, imatinib is given for 10 to 12 months, as long as there is evidence of radiological response. Patients who received neoadjuvantimatinib therapy, they should compete the course of imatinib therapy for at least 3 years (combined preoperative and postoperative). For patients presented with potentially respectable metastatic tumors with wild-type gene or without *PDGFRA* D842V mutation neoadjuvantimatinib therapy is better than upfront surgical resection [89, 90].

Finally small GIST in the proximal jejunum rarely presented with acute massive lower gastrointestinal (GIT) bleeding. We have found 7cases of jejuna GIST presented with lower GIT bleeding, most of them are large in size and also treated with exploratory laparotomy (Table 3). Our case treated via laparoscopic approach.

Table (3): Reported cases of GIST presented with lower GIT bleeding

Case	Age (year)	Sex	Size (cm)	Anatomical location	Approach	GIST subtype	Adjuvant imatinib
Javeed et al [91]	23	female	9x8x5	Jejunum	Laparotomy	Spindle cell	Yes
Srinivasan et al [92]	55	female	3x3	Jejunum	laparotomy	Spindle cell	No
Thanapal et al [93]	43	male	4.4x3.4x5	Jejunum	laparotomy	Spindle cell	No
Govindaraj et al [94]	50	female	2×2	Jejunum	laparotomy	Spindle cell	No
Daldoul et al [95]	34	male	7 ×5 × 4	Jejunum	laparotomy	Spindle cell	Yes
Shim et al [96]	44	female	3.6×2.0	Jejunum	laparotomy	Spindle cell	No
Sass et al [97]	42	female	8	Jejunum	laparoscopy	Spindle cell	Yes
Our case	34	male	2×2	Jejunum	laparoscopy	Spindle cell	No

Conclusion

Massive lower GIT bleeding is rare and atypical presentation of Jejunal GIST. CT is useful modality for diagnosis and localization of submucosal GIT tumors. Angioembolization is an essentnial diagnostic and therapeutic method in small bowel GIST presented by active bleeding but associated with high risk of

bowel necrosis. Laparoscopic small bowel resection and anastmosis is feasible in patients with small intestinal GIST coming with active lower GIT bleeding as in our case.

Abbreviations

GIST: Gastrointestinal stromal tumor

GIT: Gastrointestinal tract

PRBCs: Packed red blood cells

CT: Computed tomography

SEER: Surveillance, Epidemiology, and End Results.

ICC: Interstitial cells of Cajal

EGIST: Extraintestinal gastrointestinal tumor
CECT: Contrast enhanced computed tomography

EUS: Endoscopic ultrasound

FGG-PET: Fluorodeoxyglucose- Positron emission tomography

MRI: Magnetic resonance imaging

FNA: Fine-needle aspiration

PCR: polymerase chain reaction

TNM: Tumor, node, and metastasis

AFIP: Armed Forces Institute of Pathology

NIH: National Institutes of Health

SSG: Scandinavian Sarcoma Group

TKIs: Tyrosine kinase inhibitors

NF: Neurofibromatosis

CEUS: Contrast enhanced ultrasound

Declarations

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Ethical approval and consent to participate:

Our study exempted from ethical approval

Consent for publication:

Written consent was obtained for publication of this case report and any accompanying images.

Availability of supporting data:

All relevant data are within the paper and its Supporting Information files.

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There is no conflict of interest to disclose

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Authors' contributions:

Khaled A Sami: Study concept, design, data collection, interpretation, literature review, writing

Mohamed S Essa: Literature review, writing:

Naif A Alenazi: Data collection, writing

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Figures

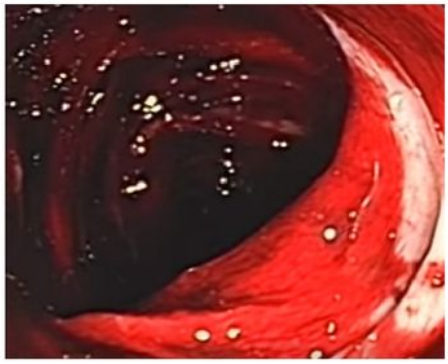


Figure 2

Colon filled with blood.

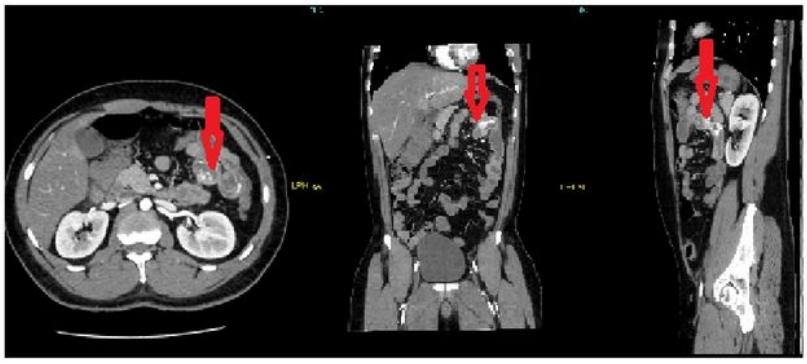


Figure 4

CT abdomen with IV contrast showed proximal jejuna mass with extravasation (red arrow).

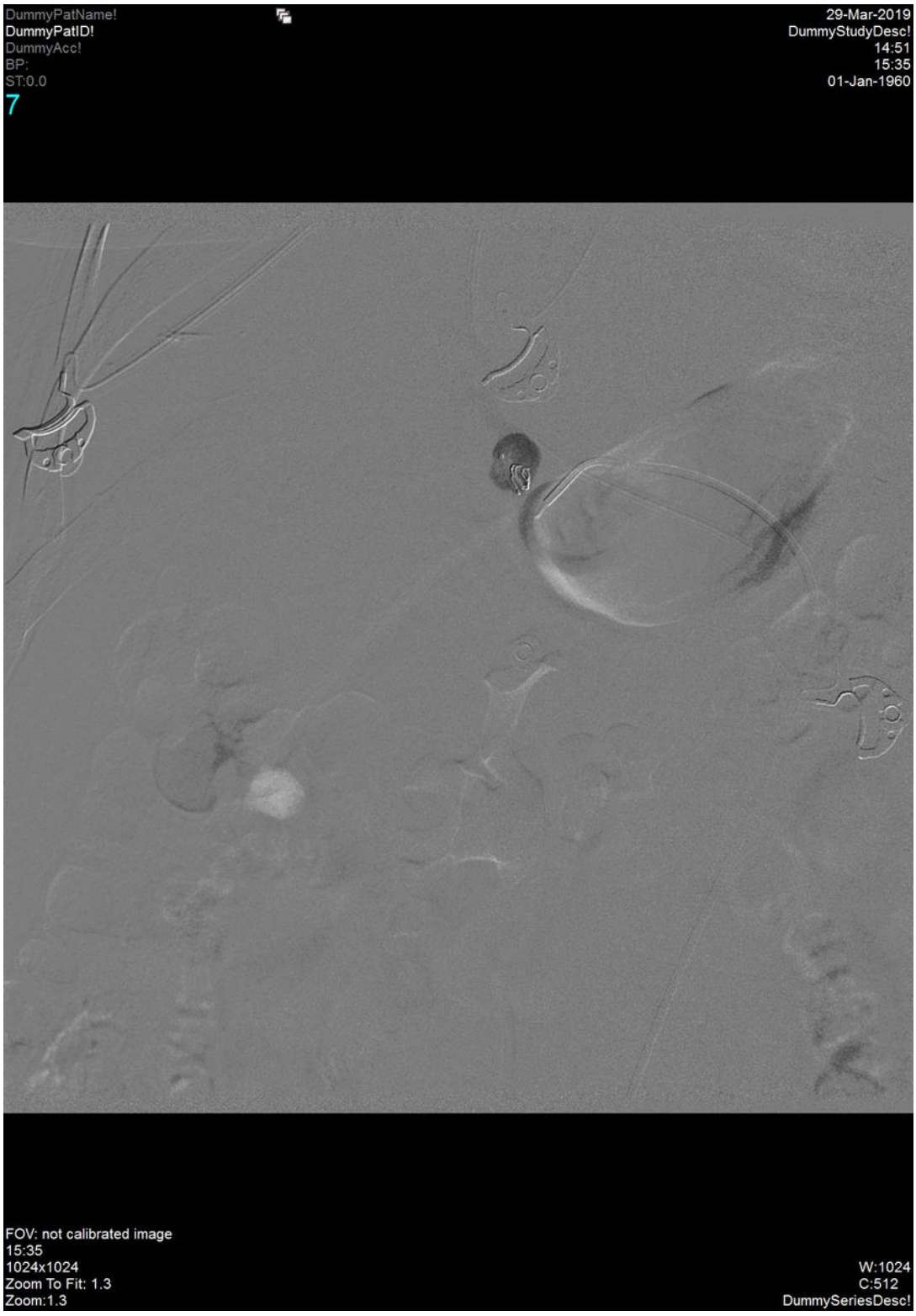


Figure 6

SMA angiography showed extravasations (yellow arrow).



Figure 8

Bowel filled with blood (red arrow).



Figure 10

GIST in proximal Jejunum (green arrow).



Figure 12

laparoscopic small bowel resection anastmosis.

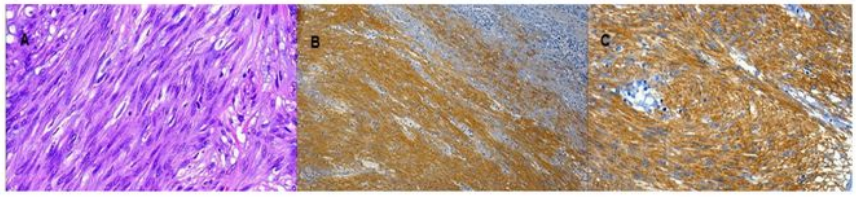


Figure 14

Spindle cell GIST, (A) hematoxylin and eosin stain (H&E), (B) KIT expression by immunohistochemistry,low magnification, (C) KIT expression, high magnification.

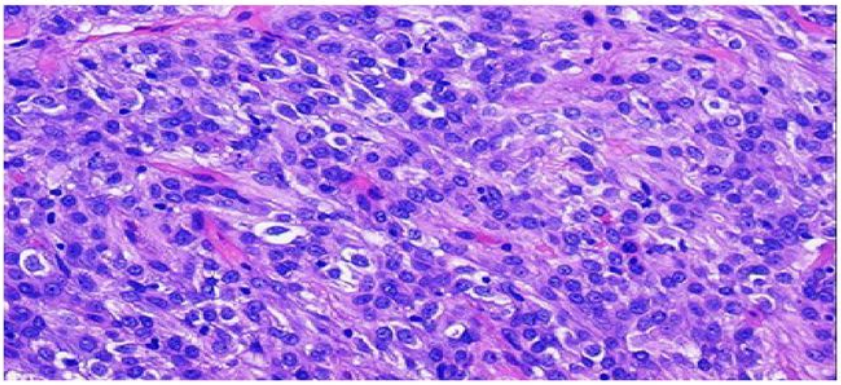


Figure 16

Epithelioid GIST, hematoxylin and eosin stain (H&E).

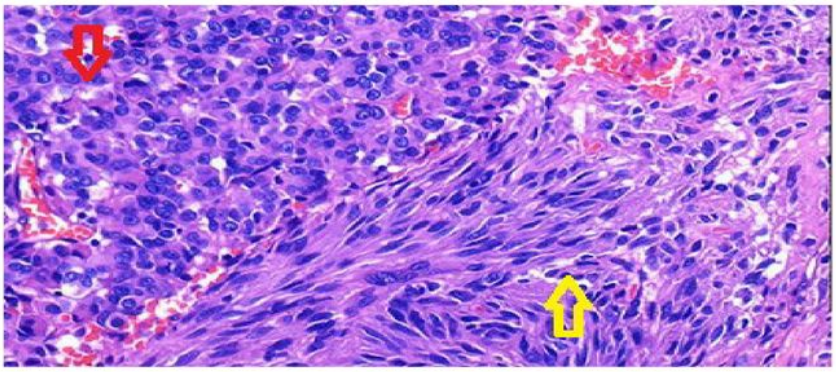


Figure 18

Mixed GIST, epithelioid component (red arrow) and spindle component (yellow arrow).