

Gastrointestinal Stromal Tumor of the Jejunum with Recurrent Bleeding: A Case Report and a Brief Literature Review

Tekrarlayan Kanamalı Jejunum Gastrointestinal Stromal Tümörü: Bir Olgu Sunumu ve Kısa Literatür Taraması

✉ Mircea Cernat¹, ✉ Ala Suman^{2,3}, ✉ Ion Vlad³, ✉ Vadim Gheorghita², ✉ Igor Mishin²

¹Oncological Institute, Department of Gastrosurgery, Chisinau, Republic of Moldova

²"N. Testemitanu" State University of Medicine and Pharmacy, Laboratory of Hepato-Pancreato-Biliary Surgery, Chisinau, Republic of Moldova

³Institute of Emergency Medicine, Chisinau, Republic of Moldova

Abstract

Bleeding from gastrointestinal (GI) stromal tumour (GIST) of the jejunum is rare and is reported in the literature as isolated clinical observations or small series. In the present study, we report a case of a 64-year-old woman who presented with recurrent GI bleeding. Upper endoscopy revealed no signs of bleeding. A contrast-enhanced computed tomography (CT) scan was performed, and a predominantly intraluminal, heterogeneous, tumour-like mass in the proximal jejunum was visualised, with dimensions 4.6x4.4x6.1 cm. A midline laparotomy was performed, and exploration of the abdominal cavity revealed a tumour in the lumen of the jejunum located 30 cm from the ligament of Treitz. Segmental resection of the jejunum with tumour, followed by anastomosis, was performed. On pathologic examination and immunohistochemistry, a spindle cell variant of GIST (c-KIT/CD117 ++++) with negative resection margins (R0) was recognised. GIST of the jejunum is a relatively rare cause of gastrointestinal bleeding. The main diagnostic method is contrast-enhanced CT. The treatment of choice for bleeding jejunal GIST is segmental resection with a negative surgical margin (R0 resection), without compromising tumor integrity.

Keywords: Small bowel, gastrointestinal stromal tumor, intermittent GI bleeding

Öz

Jejunum gastrointestinal (GI) stromal tümör (GIST) kaynaklanan kanama, nadir görülen bir kanama nedenidir ve literatürde münferit klinik gözlemler veya küçük olgu serileri şeklinde yer almaktadır. Bu çalışmada, tekrarlayan GI kanama semptomları ile başvuran 64 yaşındaki bir kadın hastanın olgusunu sunuyoruz. Üst endoskopi incelemesinde: kanama bulgusu yoktu. Kontrastlı bilgisayarlı tomografi (BT) taraması yapıldı ve proksimal jejunumda boyutları 4,6x4,4x6,1 cm olan, ağırlıklı olarak lümen içi, heterojen, tümör benzeri bir kitle saptandı. Orta hat laparotomi yapıldı ve karın boşluğunun incelenmesi sonucunda Treitz bağından 30 cm uzaklıkta jejunum lümeninde bir tümör saptandı. Tümörlü jejunumun segmental rezeksiyonu ve ardından anastomoz uygulandı. Patolojik inceleme ve immünohistokimya: rezeksiyon sınırları negatif (R0) olan GIST'nin iğ hücreli varyantı (c-KIT/CD117 +++) tanındı. Jejunum GIST'ı, GI kanamanın oldukça nadir bir nedenidir. Ana tanı yöntemi kontrastlı BT'dir. Kanamalı jejunal GIST için tercih edilen tedavi, tümörün bütünlüğünü bozmadan negatif cerrahi marjlı (R0 rezeksiyon) segmental rezeksiyondur.

Anahtar Kelimeler: İnce bağırsak, gastrointestinal stromal tümör, aralıklı GI kanama



Address for Correspondence: Prof., Igor Mishin, "N. Testemitanu" State University of Medicine and Pharmacy, Laboratory of Hepato-Pancreato-Biliary Surgery, Chisinau, Republic of Moldova

E-mail: igor.mishin2024@gmail.com **ORCID ID:** orcid.org/0000-0003-0754-7917

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Introduction

Gastrointestinal (GI) stromal tumours (GISTs) are the most frequent sarcomas of the GI tract (1-3). GISTs are most commonly localised in the stomach (50-70%), in the small intestine 32%, in the colon and rectum 6% and in the oesophagus <1% (2). GISTs of the jejunum are quite rare and account for 0.04% of all GI neoplasms (4).

Bleeding from the small intestine is quite rare and accounts for 5-10% from the whole spectrum of GI haemorrhages (5). Moreover, bleeding from GIST of the jejunum is rare and is reported in the literature as isolated clinical observations (2-4,6-18) or as small series (19). Given the low incidence of jejunal GIST as a cause of lower GI bleeding, we present our documented clinical case.

Case Presentation

A 64-year-old female was transferred from a district hospital after three days of treatment for GI bleeding of unclear aetiology. On admission, the patient complained of persistent rectal bleeding (hematochezia) for three days, weakness, and dizziness. For the last two years, the patient has experienced a similar episode of GI bleeding from an unidentified source, which was managed conservatively. Over the last six years, type II diabetes mellitus has been diagnosed and managed with drug therapy.

The patient's general condition was assessed as moderately severe. On physical examination, cutaneous pallor was noted. Respiratory rate -18/min. Heart rate -100/min. Blood pressure 110/70 mmHg. The abdomen participates in the act of breathing; no tenderness was noted. No masses are detected; the liver and spleen are not palpated. On examination per rectum, signs of blood were noted on the glove. On upper GI endoscopy examination: gastritis, no signs of bleeding.

On admission, general blood analysis: red blood cell count $2.2 \times 10^{12}/L$ (reference range, $3.3-5.5 \times 10^{12}/L$), haemoglobin 72 g/L (reference range, 120-160 g/L), haematocrit 21.1% (reference range, 35-52%), platelets $108 \times 10^9/L$ (reference range, $172-380 \times 10^9/L$), leukocytes $14.5 \times 10^9/L$ (reference range, $3.5-10.0 \times 10^9/L$), neutrophils 89.2% (reference range, 45-73%), lymphocytes 4.5% (reference range, 19-37%), monocytes 4.4% (reference range, 3-11%), eosinophils 4.9% (reference range, 0.5-5%), basophils 0.4% (reference range, 0-1%).

Biochemical tests: urea 8.5 mmol/L (reference range, 2.8-9.2 mmol/L), creatinine 61.2 $\mu\text{mol}/L$ (reference range, 44-106 $\mu\text{mol}/L$), glucose 7 mmol/L (reference range, 4.1-5.9 mmol/L), alanine aminotransferase 12.4 U/L (reference range, 0-45 U/L), aspartate aminotransferase 18 U/L (reference range, 0-35 U/L), total bilirubin 7.3 $\mu\text{mol}/L$ (reference range, 2-21 $\mu\text{mol}/L$), total protein 30.8 g/L (reference range, 66-87 g/L), albumin 19.9 g/L (reference range, 35-52 g/L), potassium 3.75 mmol/L (reference range, 3.5-5.5 mmol/L), sodium 141 mmol/L (reference range, 135-145 mmol/L), chlorine 106.8 mmol/L (reference range, 98-108 mmol/L), prothrombin 72% (reference range, 70-120%), fibrinogen 1.88 g/L (reference range, 2-4 g/L), thrombin time 16.63 sec. (<30 sec.), international normalized ratio 1.03.

The patient was admitted to the intensive care unit, haemostatic therapy was started, and a transfusion of erythrocyte mass and fresh-frozen plasma was performed. The patient's condition was stabilized, with no signs of persistent bleeding.

A contrast-enhanced computed tomography (CT) scan was performed (Figure 1A, B). In the proximal jejunum, a predominantly intraluminal, heterogeneous, tumour-like mass was visualised, with dimensions 4.6x4.4x6.1 cm and native density from +17 to +26 Hounsfield units (HU). Single punctiform calcifications are observed within the tumour. On contrast-enhanced CT scans, an increase in tumour density from

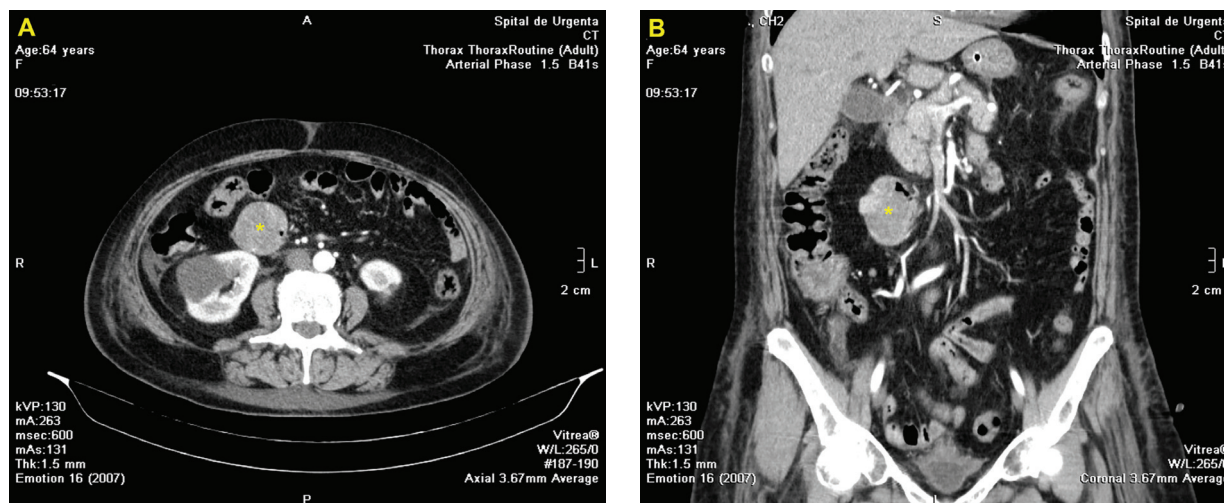


Figure 1. Computed tomography (CT) with angiography (A) axial and (B) coronal projections: a 4.6x4.4x6.1 cm solid mass in the proximal jejunum (*)

+31 to 60 HU was noted. Conclusion: jejunal tumour, most likely a GIST.

A midline laparotomy was performed. Exploration of the abdominal cavity revealed a tumour in the lumen of the jejunum at a distance of 30 cm from the Treitz's ligament (Figure 2). Segmental resection of the jejunum with tumour, followed by anastomosis was performed.

On pathologic examination, a spindle cell variant of GIST was found with low mitotic activity ($<5/50$ HPF). Immunohistochemical examination revealed diffuse cytoplasmic expression of c-KIT/CD117 in tumour cells (Figure 3), as well as diffuse expression of CD34. According to the morphological study, the resection margins were classified as R0.



Figure 2. Intraluminal tumour of the jejunum (intraoperative photo)

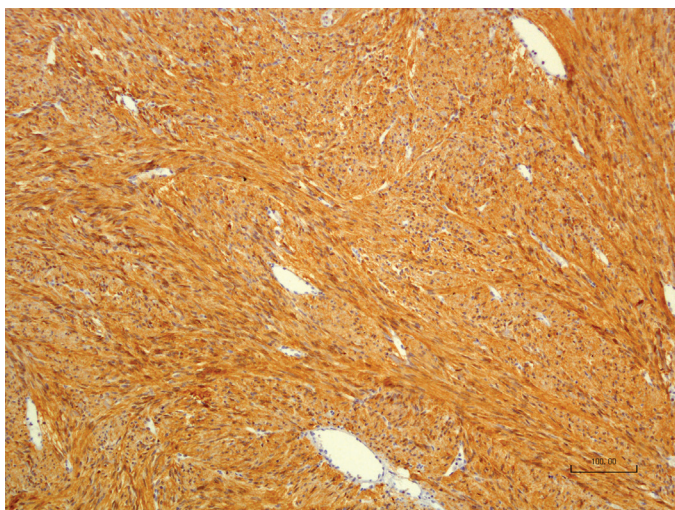


Figure 3. Immunohistochemistry: diffuse cytoplasmic expression of CD 117 (c-kit) (3,3'-diaminobenzidine x100) in tumour cells

The postoperative period was uneventful. The patient was discharged in good condition on postoperative day 14 and was referred to the Research Institute of Oncology for further treatment. The multidisciplinary team reviewed the patient and decided to initiate targeted therapy with imatinib mesylate 400 mg daily. Examined 14 months later, the patient was asymptomatic.

Oral and written informed consent was obtained from the patient to publish the patient-related data in an anonymized form.

Discussion

It is generally accepted that GIST originate from interstitial cells of Cajal or their precursors located in the muscle layer and are the pacemaker of the GI tract (1-3,15,20). GISTs are characterized by overexpression of the tyrosine-kinase receptor c-KIT and are primarily associated with activating mutations in KIT (exons 9, 11, 13, 17) and PDGFRA (exons 12, 14, 18) (3). The majority of GIST cases (70-80%) harbor a mutation in KIT gene and in less than 10% -in PDGFRA gene, otherwise 10-15% are wild-type GIST (1).

The incidence of GISTs in most studies is 1-2 cases per 100.000 populations per year (1,20). The mean age of patients with GIST is typically 60-65 years and the male to female ratio approaches 1:1 (3,12,20). In the vast majority of cases GISTs are sporadic, but in some cases these neoplasms are associated with neurofibromatosis type 1-NF1 (von Recklinghausen disease), Carney triad, Carney-Stratakis syndrome (3,9,20). An analysis of the surveillance, epidemiology, and end results database that included 702 patients with small intestinal GISTs found differences between tumors in the jejunum and ileum. Thus, compared with ileal localization, GISTs were localized significantly more often in the jejunum (67.2%), were smaller, and were observed more frequently in male patients. Traditionally, GISTs in the ileum are considered more frequent than in the jejunum, with a ratio of 60% vs. 40% (1).

The clinical manifestations of GISTs are non-specific and depend on tumor size, localization, predominant pattern of neoplasm growth (intraluminal or extraluminal), and in 20% of cases these neoplasms are asymptomatic (1,11). Clinical symptoms of GISTs include: GI bleeding (30-40%), abdominal pain (20-50%), and obstructive syndrome (10-30%) (1,13).

Factors contributing to the development of bleeding in GIST are: tumors localized in the small intestine, tumor size ≥ 5 cm, mitotic count ≥ 5 /HPF and tumor rupture (1,11,20). Nevertheless, in the literature there are descriptions of massive bleeding from smaller size intestinal GIST and low mitotic activity of the tumor (13).

The age of patients with bleeding from GISTs of jejunum ranged from 32 to 80 years (2,4,6-19) and this pathology was observed more frequently in men (2,4,6,8,10-13,15,17-19) than in women (3,7,9,14,16).

The main clinical manifestations of bleeding from a jejunal GIST are signs of acute or chronic intraluminal bleeding, including discharge of unchanged blood through the rectum (hematochezia) (7,8,11,15,18) and repeated episodes of melena and anemia (2,6,9,12-14,17). In exceptional cases, vomiting of blood was noted (4,10). Multiple episodes of bleeding from GIST of the jejunum are typical and in quite rare cases massive bleeding with hemodynamic instability of patients can be noted (10,11,13,14,16,17,19).

The issues of diagnosis and therapeutic management of bleeding from small intestinal GIST remain rather non-standardized (11). Early diagnosis of jejunal GIST is quite difficult due to inaccessibility to standard endoscopy, and often leads to delayed surgical treatment (2,4,7,11,14,15,17-19). Double-balloon enteroscopy and capsule endoscopy are the preferred methods for diagnosing the source of bleeding from the small intestine, and in case of GIST they reveal a submucosal tumor with ulceration of the mucosa above it (9,15). However, due to the exophytic component of GIST, these diagnostic methods may sometimes be non-informative (6,17).

When double-balloon enteroscopy and capsule endoscopy are not available, contrast-enhanced CT is recommended (4,7,8,11-14,16,17,19). This method allows visualization of a jejunal tumor accumulating contrast and in some cases with extravasation (8,9,13). Neirouz et al. (2) described an observation of accurate preoperative diagnosis using CT with contrast of a small bowel intussusception caused by a 2 cm jejunal tumor with recurrent bleeding. In our case, contrast-enhanced abdominal CT played the main role in establishing the preoperative diagnosis and the therapeutic management strategy.

Today, surgical resection with negative margins (R0) is the gold standard in the treatment of localized and non-metastatic GIST (3,6,13,19,20). In case of bleeding from GIST of the jejunum, it was intraoperatively found that neoplasms were localized at a distance from 15 to 170 cm from the ligament of Treitz (2,6-8,10,11,13,14,16,17). Traditionally, the surgical operation was performed through laparotomic access and the extent of surgery consisted of segmental resection of the intestine en bloc with tumor and restoration of GI passage by end-to-end or side-to-side anastomosis using both manual sutures and stapling devices (2,4,6,7,10,11,13,14,16,18). In the described case, the preferred method was open access with careful exploration of the abdominal cavity. At the same time, Saeidi et al. (17) described an observation of the use of damage control principle in massive, life-threatening bleeding from GIST of the jejunum.

Due to the failure of hemodynamically stabilize the patient with high doses of inotrop and vasopressor support, only the resection stage was performed at the first, and 48 hours later, after complete stabilization of the patient, the final stage was performed-restoration of GI passage (17). A mandatory condition during surgeries for GIST is to preserve the integrity of the tumor pseudocapsule to prevent its recurrence (1,6,20). At the same time, lymph node dissection was not performed due to the extremely rare metastasis of GIST to lymph nodes (1,3,6). In a number of reports on jejunal GIST, surgical interventions were performed using laparoscopic techniques (8,9,15,19). Huynh and Rust (12) described an observation of successful resection of proximal jejunal GIST using robotic technique, in which bowel resection and subsequent intracorporeal anastomosis were performed using staplers, and the adequacy of intestinal perfusion was assessed using indocyanine green.

Macroscopically, jejunal GIST represents a lobular tumor of gray color spreading from the submucosal layer to the serosa of the intestine with significant extraluminal growth (4,6-8,10,11,13,14,16,18) and with sizes ranging from 2 cm to 9 cm (2,4,6,9-11,14,16,17). The main cause of bleeding in GIST of the jejunum is necrosis and ulceration of the mucosa as a result of the compression effect of the tumor on the intestinal wall (6,8,9,11,13,14).

Histopathologic examination revealed a spindle cell variant of GIST in the majority of cases (8,10,13,14,16,18) and extremely rare epithelioid (9) and mixed variants (7,17). This pattern is observed for GIST of all localizations, where the spindle cell tumor variant is the most frequent (77%) and in smaller proportions-the epithelioid (8%) and mixed types (15%) (1,3).

According to immunohistochemical study, positive expression in tumor cells for CD117/c-KIT (4,6-13,16-18), DOG-1 (4,6,9-12,14,16-18), CD34 (9,11,13,14,18) and negative reaction for desmin (4,10), smooth muscle actin (10), CD34 (16) was established. When proliferative activity was evaluated, <5 mitoses/5 mm² was noted (2,6,8,9,12,13,15-18).

As adjuvant therapy imatinib (a tyrosine kinase receptor inhibitor) in the regimen of 200-400 mg/day was used (7,9,10). It was found that imatinib was effective in cases harboring a mutation in exon 11 of the *c-KIT* gene, whereas a mutation in exon 9 may produce a response to targeted therapy only at higher drug doses. In the absence of mutations in the *c-KIT* gene, resistance to imatinib is observed (3,20).

The absence of tumor recurrence and metastases was noted within the follow-up period from 3 months to 6 months after surgical treatment (6,9). Prognostic factors in GIST are: tumor localization and size, the number of mitoses, as well as the presence of neoplasm rupture (17,20). According to international guidelines the risk of recurrence in our case was 3a (moderate

risk) and the patient started targeted treatment with imatinib mesilat (20).

Conclusion

GIST of the jejunum is a rather rare cause of GI bleeding. The main diagnostic method is contrast-enhanced CT. The treatment of choice for bleeding jejunal GIST is segmental resection with a negative surgical margin (R0 resection), performed without compromising tumor integrity, to prevent local recurrence and possible metastasis.

Ethics

Informed Consent: Oral and written informed consent was obtained from the patient to publish the patient-related data in anonymized form.

Footnotes

Authorship Contributions

Concept/Design: M.C., I.M., Data Collection or Processing: A.S., I.V., V.G., Analysis or Interpretation: M.C., I.M., Literature Review: M.C., A.S., I.V., V.G., I.M., Writing, Reviewing and Editing: M.C., A.S., I.V., V.G., I.M.

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