A Sporadic Small Jejunal GIST Presenting with Acute Lower Gastrointestinal Hemorrhage: A Review of the Literature and Management Guidelines

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Abstract Gastrointestinal stromal tumors (GISTs) represent the majority of primary nonepithelial neoplasms of the digestive tract, most frequently expressing the KIT protein detected by immunohistochemical staining for the CD117 antigen. Jejunal GISTs account for approximately 10 % of GISTs. Patients usually present with abdominal discomfort. Jejunal GISTs may cause symptoms secondary to obstruction or hemorrhage. Pressure necrosis and ulceration of the overlying mucosa may cause gastrointestinal bleeding, and patients who experience significant blood loss may suffer from malaise and fatigue. Literature has classified small-bowel GISTs on the basis of size, and various established guidelines have advised conservative management of small jejunal GISTs (<2 cm). We here report the clinical, macroscopic, and immunohistological features of a small jejunal GIST presenting with acute lower gastrointestinal hemorrhage in a 50-year-old postmenopausal woman necessitating an emergency laparotomy to control the bleed. The management of very small (<2 cm) small-bowel GISTs is controversial. While guidelines are primarily based on the risk of malignancy in GISTs, no guideline predicting the risk of complications in small-bowel GISTs exists. Hence, these tumors should be removed even if incidentally detected.

Keywords Jejunal GIST · GIST · Lower GI bleed

A gastrointestinal stromal tumor (GIST) is a visceral tumor arising from any site of the gastrointestinal tract. The most common site of presentation is the stomach, but it can crop up anywhere in the digestive tract. Two thirds of GISTs occur in the stomach [1], while about one fourth develop in the small intestine, usually in the duodenum. GISTs are uncommon mesenchymal neoplasms of the alimentary tract. The incidence of GIST is very low (i.e., 2 in 100,000), while jejunal GIST is extremely rare, accounting for 0.1–3 % of all gastrointestinal (GI) tumors [2]. Depending on tumor size, small-bowel GISTs less than 2 cm can be classified as small GISTs [3]. The most common symptoms associated with jejunal GISTs are vague, nonspecific abdominal pain or discomfort. Pressure necrosis and ulceration of the overlying mucosa may cause gastrointestinal bleeding. We present a case of a very small jejunal GIST presenting with massive gastrointestinal hemorrhage.

Case Report

A 50-year-old postmenopausal lady presented to the department of emergency medicine with acute-onset fatigue associated with melena of 2 days duration and hematochezia since 1 day. She had no previous history of gastrointestinal bleeding and her family history was negative for familial cancer syndromes. Her general physical examination was negative for café au lait spots or macules, and her thyroid and neck

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examination was normal. Her hemoglobin had dropped from 14 to 7 g/dL and was referred to us as a colonoscopy, and esophagogastroduodenoscopy failed to identify the source of bleed. She was immediately admitted and transfused two units of packed red cells, and a CT mesenteric angiogram was done which revealed a 2×2-cm enhancing mass lesion in the jejunum (Fig. 1). On CECT, the adrenal glands were found to be normal and there was no evidence of any extraintestinal mass lesions. In view of the persisting drop in hemoglobin levels, the patient was taken up for an emergency laparotomy. On laparotomy, a 2×2-cm firm growth was found to be arising from the antimesenteric border of the jejunum around 30 cm distal to the duodenojejunal flexure. The vessels supplying the growth appeared dilated and thin walled. No regional lymph node was enlarged. No peritoneal deposits could be found. The growth was resected with the segment of jejunum containing it with an adequate free margin of 5 cm, and end-to-end anastomosis of the jejunum was done. The patient improved dramatically after surgery and her hemoglobin level stabilized at 11 g/dL. The postoperative recovery was uneventful and the patient is doing fine after 3 months of follow-up.

On gross examination, a 2×2-cm nodular growth was seen to be arising from the resected jejunal segment with a gray white external surface. The mucosal surface was ulcerated. On sectioning, the growth was well circumscribed, submucosal, and had a homogenous gray white cut surface. On microscopy, a well-circumscribed submucosal neoplasm involving the entire wall thickness was noted. Spindle-shaped neoplastic cells arranged as interlacing fascicles were seen. The cells showed moderate amount of eosinophilic cytoplasm with an elongated nucleus with blunt ends. The adjacent stroma showed mild to moderate lymphocytic infiltration. There

was no evidence of necrosis/atypia. The mitotic count was 2/50 hpf. Immunohistochemistry markers for CD117, SMA, CD34, S-100, chromogranin, and Ki67 were done. The neoplastic cells were found to be positive for CD117 (3+, 90 %), SMA (2–3+, 60–70 %), and CD34 (3+, 70 %) and were negative for S-100 and chromogranin. The Ki67 index was less than 5 % (Fig. 2), which was suggestive of a benign GIST.

We also checked for platelet-derived growth factor receptor- α (PDGFRA) mutation as this is an upcoming marker in the management of GISTs. Our case was negative for platelet derived growth factor receptor alpha (PDGFRA).

Discussion

Primary mesenchymal tumors of the digestive tract can be divided into the following major categories according to their phenotypic features: tumors with differentiation toward smooth muscle cells [smooth muscle actin (SMA) positive]; those with neural differentiation (S-100 and/or chromogranin positive); those with histiocytes, a small group toward smooth muscle and nerve; and those with no differentiation [4, 5]. Approximately 80 % of GISTs have an oncogenic mutation in the KIT tyrosine kinase [1]. Most of these mutations affect the juxtamembrane domain encoded by *KIT* exon 11, allowing spontaneous (ligand-independent) receptor dimerization and kinase activation. However, mutations also occur in exons 9, 13, and 17, and these may support constitutive KIT signaling through other mechanisms. A subset (5–7 %) of GISTs has an activating mutation in the KIT-homologous tyrosine kinase PDGFRA. *PDGFRA*-mutant GISTs have an epithelioid morphology and express little or no KIT; however, such features

Fig. 1 a, b CT mesenteric angiogram showing an enhancing lesion just below the left kidney. c, d Jejunal hyperenhancing lesion seen on cross-sectional images

**A. and B. CT MESENTERIC ANGIOGRAM SHOWING AN ENHANCING LESION JUST BELOW THE LEFT KIDNEY
C. and D. JEJUNAL HYPERENHANCING LESION SEEN ON CROSS SECTIONAL IMAGES**

Fig. 2 EGIST of the greater omentum: *I* intraoperative photograph showing jejunal GIST, *II* tumor cells in high power (H & E $\times 400$), *III* tumor cells showing CD34 positivity, and *IV* tumor cells showing CD117 positivity

EGIST OF THE GREATER OMENTUM: I. Intraoperative photograph showing jejunal GIST; **II.** Tumour cells in high power (H & E $\times 400$); **III.** Tumour cells showing CD34 positivity; **IV.** Tumour cells showing CD117 positivity.

are not unique to these tumors, and mutation status can be determined only through molecular analysis. About 10 to 15 % of GISTs are negative for *KIT* and *PDGFRA* gene mutations; these tumors are often referred to as *wild-type GISTs*. In our case, we had a spindle cell tumor negative for *PDGFRA* and positive for CD117 and CD34. Many of these immunohistochemical features of GISTs are also very important for the differential diagnosis between the various types of submucosal tumors, such as schwannomas, and neuroendocrine tumors. Digestive tract schwannomas are S-100 protein and vimentin positive, never express the CD117 antigen, and are usually negative for CD34, in contrast to GISTs [1]. Schwannomas are also negative for SMA.

Various unusual forms and variants of the GISTs have been described, including jejunal GIST. Immunocytochemical studies showed KIT (CD117) and CD34 immunopositivity, attributes that are restricted in the gut to the interstitial cells of Cajal [5]. The interstitial cells of Cajal are mesodermal derivatives that become associated with the autonomic myenteric plexus during development and are thought to regulate peristalsis [5]. Today, the majority of alimentary tract intramural tumors are interpreted as GISTs, including tumors formerly referred to as gastrointestinal autonomic nerve (GAN) tumor and plexosarcoma. Activating mutations of the *KIT* gene are often found in GISTs. GISTs also show strong site-dependent genetic heterogeneity [5]. The tumor is a major or minor component of certain rare syndromes and familial and nonfamilial functioning paraganglioma, and GISTs are uncommon tumors that occur mostly in a sporadic and isolated form, occasionally as components of multiple neoplasia syndromes, either separately or together. Separately, they occur in several inherited syndromes including multiple

endocrine neoplasia [5], the GIST, lentiginos, and mast cell tumor syndrome. Together, they are variably prominent components of three syndromes: the familial paraganglioma and gastric GIST syndrome, neurofibromatosis type 1, and the Carney triad (syndrome with paraganglioma-jejunal GIST combination). The two former conditions are inherited as autosomal dominant traits; the latter does not appear to be inherited and affects young women predominantly [5].

Imatinib mesylate is a selective, potent, small-molecule inhibitor of a family of structurally related tyrosine kinase-signaling enzymes, including (1) KIT; (2) the ABL family of tyrosine kinases, including the leukemia-specific BCR-ABL chimera; and (3) PDGFR. It has been long used in the treatment of GISTs with KIT positivity. The first GIST patient to receive imatinib was a 50-year-old woman, with KIT-positive metastatic GIST associated with a mutation in exon 11. She had progressive metastatic disease despite surgery, combination cytotoxic chemotherapy, thalidomide and interferon alpha. She was treated with 400 mg of imatinib per day, and response was evaluated using 18-fluorodeoxyglucose positron emission tomography (18-FDG PET) and CT scanning. After 1 month, the patient had a complete metabolic response, and by 8 months, many of the liver metastases had disappeared or reduced in size [6]. A dose of 400 mg OD is the recommended dose of imatinib in the treatment of GISTs. The success of imatinib in controlling locally advanced and metastatic GIST has led to interest in the neoadjuvant and adjuvant use of the drug. Currently, neoadjuvant imatinib is not recommended where a change in tumor size will not affect surgery. It can, however, be considered where a tumor response could permit function-sparing surgery, e.g., rectum or esophagus. There has also been significant interest in the use of imatinib in the adjuvant setting. This stems

from the successes of treatment of advanced disease with the rationale that it may be more effective in minimal residual disease and may be curative in this setting. In high-risk patients, the rates of recurrence after primary surgery are about 50 %. Prospective trials are running to assess the role of imatinib following surgery for high-risk GIST. Two types of resistance to imatinib treatment exist: primary resistance (on initial use of the drug) and secondary resistance (after an initial response). Ten to fifteen percent of patients are primarily resistant to treatment with imatinib.

A review on GISTs by Rammohan A et al. [3] classified GISTs on the basis of size. They also stated that very small asymptomatic GISTs (less than 2 cm) can be managed conservatively. The American Gastroenterological Association recommends removal of all GISTs with diameter ≥ 3 cm [7]. The National Comprehensive Cancer Network recommends removal of all GISTs with size ≥ 2 cm [8], whereas the European Society for Medical Oncology recommends removal of all GISTs >2 cm [9]. The 2-cm cutoff in these guidelines is based on the malignancy risk stratification for GISTs proposed by Miettinen M. et al. [10]. The treating team of surgeons and gastroenterologists should understand that there is no guideline predicting the risk of bleeding and other complications associated with small-bowel GISTs. Hence, the 2-cm cutoff proposed in the said guidelines need not apply to the incidence of complications as well. In our case, we have reported a very small jejunal GIST that has presented with massive gastrointestinal hemorrhage. Hence, the role of conservative treatment in small-bowel GISTs is questionable. In our opinion, incidentally detected small-bowel GISTs need to be operated upon irrespective of their size at the time of detection, as these tumors can present as acute emergencies at a later date.

Conclusion

The management of very small (<2 cm) small-bowel GISTs is controversial. While guidelines are primarily based on the risk of malignancy in GISTs, no guideline predicting the risk of

complications in small-bowel GISTs exists. Hence, these tumors should be removed even if incidentally detected.

Conflict of Interest The authors declare no conflict of interest.

References

1. Miettinen M, Sobin LH, Lasota J (2005) 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* 29(1):52–68
2. Kramer K, Siech M, Sträter J, Aschoff AJ, Henne-Bruns D (2005) 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* 43(3):281–288
3. Rammohan A, Sathyanesan J, Rajendran K, Pitchaimuthu A, Perumal SK, Srinivasan UP et al (2012) A gist of gastrointestinal stromal tumors: a review. *World J Gastrointest Oncol* 5(6):102–112
4. Miettinen M, Virolainen M, Sarlomo-Rikala M (1995) Gastrointestinal stromal tumours—value of CD34 antigen in their identification and separation from true leiomyomas and schwannomas. *Am J Surg Pathol* 19:207–216
5. Perry CG, Young WF Jr, McWhinney SR, Bei T, Stergiopoulos S, Knudson RA et al (2006) Functioning paraganglioma and gastrointestinal stromal tumor of the jejunum in three women: syndrome or coincidence. *Am J Surg Pathol* 30(1):42–49
6. Joensuu H, Roberts PJ, Sarlomo-Rikala M et al (2001) Effect of the tyrosine kinase inhibitor STI571 in a patient with a metastatic gastrointestinal stromal tumor. *N Engl J Med* 344:1052–1056
7. Hwang JH, Rulyak SD, Kimmey MB (2006) American Gastroenterological Association Institute technical review on the management of gastric subepithelial masses. *Gastroenterology* 130: 2217–2228
8. Demetri GD, VonMehren M, Antonescu CR, DeMatteo RP, Ganjoo KN, Maki RG et al (2010) NCCN Task Force report: update on the management of patients with gastrointestinal stromal tumors. *J Natl Compr Canc Netw* 8(Suppl 2):S1–S41
9. Casali PG (2008) Gastrointestinal stromal tumors: ESMO clinical recommendations for diagnosis, treatment and follow-up. *Ann Oncol* 19(2):ii35–ii38
10. Miettinen M, Lasota J (2006) Gastrointestinal stromal tumors: pathology and prognosis at different sites. *Semin Diagn Pathol* 23:70–83