Gastrointestinal Stromal Tumours: A Series of 12 Cases

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Abstract Gastrointestinal stromal tumour (GIST) is a soft tissue sarcomas arising from interstitial cell of Cajal of the gastrointestinal tract. Since its description in 1983, its management has seen sea change - from surgery to drug therapy, for CD 117 positive patients. Though it has an indolent course compared to adenocarcinoma, over the decades it has surprised surgeons with its varied presentation. We report a series of 12 cases of GIST. These were evaluated with respect to their age, gender, clinical presentation, histopathology grade, treatment offered & final outcome. There were 7 gastric, 1 duodenal, 1 sigmoid, 1 rectal & 2 retroperitoneal GISTs. Resection was carried out for 8 GISTs, 1 was enucleated, 2 are on imatinib therapy & one is under observation. All operated patients had an uneventful post-operative recovery.

Keywords GIST · Imatinib

Case 1

A 51-year-old woman presented with a gradually increasing upper abdominal lump for 1 year. CT scan of abdomen revealed an ovulated (6 cm×4 cm×3 cm) mass postero-inferior to greater curvature of stomach with well-maintained fat planes. Endoscopic ultrasonography (EUS) was carried out which showed that the mass was arising from muscularis propria (Fig. 1). Fine needle aspiration cytology (FNAC) reported it as leiomyoma. The tumor was excised along with a part of stomach wall. The histopathology examination (HPE) showed that the tumor consisted of spindle cells arranged in fasciculus and interlacing bundles, suggestive of GIST. Resection margins were free.

Case 2

A 65-year-old woman presented with hematemesis. The patient was resuscitated and upper GI endoscopy was carried out which revealed a submucosal mass along the greater curvature of stomach (Fig. 2). CT scan was suggestive of a well-defined heterogeneously enhancing endoluminal polypoidal (5.5 cm×4.8 cm) mass lesion along the greater curvature of the stomach of neoplastic etiology. The patient underwent total gastrectomy with Roux-en-Y esophagojejunostomy. HPE was suggestive of gastrointestinal stromal tumor (GIST) and resection margins were free. Post-operative course was uneventful and the patient has been recurrence-free for 2 years.

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Fig. 1 EUS finding of a large intragastric submucosal mass suggestive of GIST

Case 3

A 45-year-old woman presented with dull aching continuous upper abdominal pain. Examination revealed a smooth globular lump in the epigastrium. Abdominal CT scan showed a (6 cm×4 cm) well-defined intramural mass along the greater curvature of the stomach. Upper GI endoscopy and biopsy confirmed diagnosis of GIST (Fig. 3). Sleeve gastrectomy with excision of mass was performed. On final HPE resection margins were free. The patient was free of recurrence at 2 years of follow-up.

Case 4

A 60-year-old woman presented with recurrent epigastric pain. Abdomen examination was unremarkable. Upper GI scopy showed a polypoidal growth at fundus and the biopsy taken was suggestive of GIST (Fig. 4). The patient underwent upper partial gastrectomy and esophagogastrostomy. HPE confirmed the diagnosis, and resection margins were free. The patient was free of recurrence at 3 years of follow-up.

Fig. 2 An endoscopic view of a gastric GIST

Fig. 3 A postoperative specimen of a gastric GIST

Case 5

A 48-year-old man presented with an abdominal lump. CT scan abdomen showed a well-defined intra-luminal mass (6 cm×4 cm) arising from greater curvature of the stomach. Upper GI scopy showed a polypoidal growth arising from antrum and biopsy report was suggestive of GIST. The patient underwent partial gastrectomy with gastrojejunostomy. The HPE was suggestive of GIST and resection margins were free. There was no recurrence after 18 months of follow-up (Fig. 5).

Case 6

A 24-year-old man presented with an epigastric lump and pain for 1 year. Abdominal CT scan was suggestive of a (11 cm×8 cm) lesion arising from the left lobe of liver suggestive of hydatid cysts. Exploratory laparotomy was carried out. After separating the lump all over, it was found that the lump was actually arising from lesser curvature of the stomach. Sleeve gastrectomy with excision of lump was carried out. The HPE was suggestive of GIST with 6–7 mitoses/50 hpf. Resection

Fig. 4 An endoscopic view of a gastric GIST

Fig. 5 **a** CT scan picture showing intraluminal gastric mass, **b** endoscopy showing the same, and **c** post-operative specimen

margin was positive. Immunohistochemistry marker for CD117 was positive. The patient was started on imatinib. FDG-PET scan was carried out which suggested increased uptake along lesser curvature of the stomach. The patient was re-explored after 6 months and completion gastrectomy was done. The patient was continued on imatinib for 6 months. Repeat FDG-PET was normal (Fig. 6).

Case 7

A 50-year-old man was referred from a peripheral center in view of intestinal obstruction. Abdominal CT scan was suggestive of colo-colic intussusception. There was no lymphadenopathy and the liver was normal. Resection of the involved segment with Hartmann's colostomy was done. The final HPE was GIST. Resection margins were free. The patient was started on imatinib. Stoma closure was done after 1 year. At 2-year follow-up he is disease free (Fig. 7).

Case 8

A 68-year-old man presented with complaints of constipation, intermittent colicky lower abdominal pain, and bleeding per rectum. The patient had right total hip replacement 1 year back. Abdominal examination was normal, but on rectal

examination there was a smooth globular palpable growth on the right side about 7–8 cm from the anal verge. Colonoscopy confirmed the findings and biopsy suggested GIST. CD 117 was negative. The patient was offered surgery and probable requirement of temporary or permanent stoma was explained. The patient refused surgery and hence was kept under observation. Patient's symptoms aggravated 1 year later, and he gave consent for surgery. Exploratory laparotomy with enucleation of GIST and temporary loop transverse colostomy was done. Post-operative course was uneventful and the patient is awaiting stoma closure. The final histopathology report showed low-grade GIST (Fig. 8).

Case 9

A 63-year-old man presented with complaints of a gradually progressing lump and feeling of discomfort in the abdomen. He had history of being operated for jejunal GIST 4 years back. Postoperatively he was advised to take imatinib which he refused. Subsequently, he lost 12 kg of weight and hemoglobin was 5.5 gm%. USG-guided biopsy was done which was suggestive of high-grade GIST. CT abdomen was suggestive of a large retroperitoneal mass. The patient was started on imatinib, and now after 1 year of follow-up he is symptomatically better, has gained weight, and hemoglobin is 9.8 gm% (Fig. 9).

Fig. 6 **a** A CT scan showing a large mass arising from the left lobe of liver and **b** the mass actually arising from the stomach (the liver looks normal)

Fig. 7 **a** Barium enema showing typical “claw sign” suggestive of intussusception and **b** postoperative specimen

Case 10

A 24-year-old man presented with a lump in the abdomen, weight loss, and anorexia for past 4–5 months. He was operated for a similar lump 2 years back. Examination revealed a lump in the right hypochondriac region extending up to the right iliac region. It was nontender and nonmobile. CT scan was suggestive of a large mass (15 cm×10 cm×10 cm) arising from the retroperitoneum and reaching up to the anterior abdominal wall. It was impinging on the inferior border of the liver. Right subcostal incision was taken. The mass was adherent to the anterior abdominal wall and the liver. It was also adherent to colon and jejunum. The mass was separated from the liver and resected along with part of transverse colon and jejunum. Colo-colic and jejuno-jejunal anastomosis were done. The histopathology report confirmed intermediate-grade GIST. CD 117 was positive. Postoperative course was uneventful. He was started on imatinib, and after 4 years of follow-up there is no recurrence (Fig. 10).

Case 11

A 56-year-old vendor presented with an epigastric lump and early satiety for past 2 months. CT scan was suggestive of multifocal intragastric exophytic lesions. Upper GI endoscopy and biopsy suggested CD 117-positive GIST. The patient was started on imatinib and kept under observation (Fig. 11).

Case 12

A 60-year-old man had undergone upper GI scopy for dysphagia and had incidental finding of a small (1 cm×1 cm) mass suggestive of GIST in the second part of duodenum. The patient is under observation (Fig. 12).

Discussion

GISTs are rare malignancies. Although they are the most common sarcomas of the gastrointestinal (GI) tract, they

Fig. 8 A solitary rectal mass with smooth margins suggestive of rectal GIST

Fig. 9 An operated case of jejunal GIST with peritoneal recurrence

Fig. 10 **a** Lump before the first surgery), **b** lump after recurrence, **c** intra-operative presentation, and **d** postoperative specimen

represent only 0.2 % of all GI tumors [1, 2]. GISTs are defined as tumors of mesenchymal origin which are due to mutations in *c-kit* gene. More than 95 % of GISTs express CD 117 receptor. GISTs arise from interstitial cells of Cajal (ICC), which are normally a part of the automatic nervous system of the intestine [3].

Until the late 1960s, stromal tumors arising in the GI tract were referred to as smooth muscle neoplasms of the GI tract. Immunohistochemistry in the 1980s demonstrated that some of these tumors lacked features of smooth muscle differentiation, some had markers of neuronal differentiation, and some had neither of the above markers. This led Mazur and Clark to coin the general term “gastrointestinal stromal tumors” in 1983 to collectively refer a group of mesenchymal tumors of neurogenic or myogenic differentiation [4]. In 1998, discovery of *c-kit* gene mutation by Hirota and colleagues led to introduction of a chemotherapeutic agent “imatinib mesylate,” a tyrosine kinase inhibitor for *c-kit*, as a therapeutic tool for

management of GIST [5]. The advent of effective chemotherapy for GIST has altered, but not diminished the role of surgery for this disease.

Clinical presentation is variable. Primary GISTs can arise throughout the GI tract, but are most common in the stomach (40–70 %), followed by small bowel (20–40 %) and colorectum (5–15 %), and rarely found in the esophagus (5 %) [6]. GISTs are usually present in patients from 40 to 60 years of age and distributed equally in men and women. Many patients with GIST are asymptomatic, discovered on imaging or at laparotomy for other reasons. Patients with advanced disease may present with an abdominal lump or vague abdominal pain. Sometimes it presents with complications such as the following:

1. Intraluminal or intraperitoneal bleeding due to its rupture (hematemesis, melena, shock) and this complication carries a high risk of dissemination by peritoneal seeding of the tumor

Fig. 11 **a** CT scan before starting imatinib and **b** 3 months after imatinib therapy

Fig. 12 A small duodenal GIST

2. Obstruction of the GI tract
3. Compression of biliary radicles leading to obstructive jaundice
4. Metastatic disease (<5 %)

GIST is a histological diagnosis. Endoscopy or image-guided biopsy is taken. The tumor typically arises from muscularis propria and shows spindle cells. When diagnosis is suspected, immunohistochemistry marking for CD117 is done which is positive in more than 95 % of cases. CT scan is required to determine the anatomic extent of the GIST and to assist with operative planning. CT is a diagnostic modality of choice. The contrast study typically shows peripheral enhancing pattern suggestive of the viable tumor in peripheral area. Central area of low attenuation corresponds to hemorrhage, necrosis, or cyst formation [7]. Calcification is uncommon [8]. CT scan also differentiates GIST from lymphomas or adenocarcinomas which are usually associated with lymphadenopathy.

MRI is a useful adjuvant for CT scan. The degree of necrosis and hemorrhage greatly affects the signal intensity pattern. The solid portion of the tumor has low-signal intensity on T1WI and high-signal intensity on T2WI and enhancement on gadolinium administration [9, 10].

F-fluorodeoxyglucose (FDG)¹⁸ positron emission tomography (PET) is complementary to the information obtained by conventional anatomic imaging. An actual mechanism responsible for the high-level avidity of GISTs for FDG tracer is not known. Postulated mechanism is that there is direct connection between signaling through the overactive KIT, TK, and glucose transport proteins. Rapid changes in PET imaging are associated with inhibition of KIT signaling by pharmacologic means. Thus, 18FDG-PET can provide functional information about the response of a tumor to treatment. It is the best investigation to follow the patient on molecular targeted therapy [11, 12].

Endoscopic ultrasound is helpful for upper GI and colorectal GIST. EUS-guided biopsy can also be done.

Table 1 shows the risk category of gastrointestinal stromal tumors.

The core of management of GIST is surgical resection for all resectable GISTs. The reported resectability rate for localized primary GIST is 70–80 % [13–15]. Clear resection margins are important. Tumor rupture or any other violation of the tumor pseudocapsule is associated with an increased risk of recurrence, including risk of dissemination of the tumor throughout the peritoneum. If the lesion involves adjacent organs, en bloc resection is considered essential to avoid tumor spillage. Small lesions (<1 cm) involving esophagus and duodenum may be observed with 6-monthly follow-up. Endoscopic resection of small lesions remains controversial because of the risk of incomplete margins and the possibility of tumor spillage during manipulation of these lesions that are sometimes very friable.

All unresectable, recurrent, and metastatic GISTs are considered for imatinib therapy. Although initial disease response is rapid, the median time to an objective response is approximately 6 months [16]. Complete responses are rarely seen. The short-term prognosis is relatively good for patients who achieve even response with imatinib. The 2-year survival for these individuals is approximately 85–90 % [17].

Sunitinib malate is a second-generation tyrosine kinase inhibitor, approved by FDA (2006), for therapy of GIST patients who failed to respond to imatinib therapy. The effects are associated with blockage of receptor tyrosine kinase signaling by KIT, PDGFRs, all three isoforms of the vascular endothelial growth factor receptors (VEGFR-1, VEGFR-2, and VEGFR-3), fms like tyrosine kinase-3 receptor (FLT3), and the receptor encoded by the ret protooncogene (RET) [18]. Sunitinib and imatinib bind with the ATP-binding domain of the KIT and PDGFRs although they are the member of different chemical classes and presumably have different binding characteristics and affinities. In GIST, sunitinib exerts an anti-angiogenic effect via inhibition of VEGFRs and PDGFR, while its anti-tumor properties are through inhibition of KIT and PDGFRA as with imatinib, KIT mutation status appears to be a predictor of response to sunitinib [19].

Constitutively activating mutations of KIT are often present in GIST, and result in increased cell proliferation and enhanced

Table 1 Classification of primary gastrointestinal stromal tumors by risk of metastasis

Risk category	Size	Mitotic count
Very low risk	<2 cm	<5/50 hpf
Low risk	2–5 cm	<5/50 hpf
Intermediate risk	<5 cm	6–10/50 hpf
	5–10 cm	<5/50 hpf
High risk	>5 cm	>5/50 hpf
	>10 cm	Any count
	Any size	>10/50 hpf

cell survival. Mutations occur most commonly in the juxtamembrane exon 11 of the gene (in 65 % of all GISTs), whereas 10 % of GISTs have KIT exon 9 mutations and 2 % exon 13 or exon 17 mutations [20]. Approximately 5 % of GISTs have a constitutively activating mutation in PDGFRA [21]. KIT and PDGFRA mutations appear to be mutually exclusive; GISTs with a mutation in both of these genes do not exist or are very rare. Most (80 %) PDGFRA mutations are found in exon 18, and the rest either in exon 12 (10–15 %) or in exon 14 (1–5 %). The response to imatinib can be predicted on the presence and location of mutation in KIT or PDGFRA. GISTs harboring the most common KIT exon 11 mutation show nearly 67–85 % response, while GISTs with exon 9 mutation show 45 % response [22]. In contrast, GISTs with most common PDGFRA exon 18 mutation show no response to imatinib, whereas other PDGFRA mutants show variable response. The recent studies have shown that mutational screening may also be helpful for predicting the optimal dose of imatinib. GISTs which harbor KIT exon 9 mutation show significantly longer progression-free survival with high-dose imatinib (800 mg/day). The other KIT or PDGFRA mutation has no impact of dose greater than 400 mg/day.

Preliminary data also show that KIT exon 9 mutant GISTs are more sensitive to sunitinib than those with exon 11 mutations.

Surgery has an important role in palliation of such patients. Large lesions that produce significant symptoms such as pain or early satiety should be considered for surgical therapy even if the symptomatic lesion is incompletely respectable or occurs in the presence of metastatic disease. Surgery is also required for patients presenting with complication of GIST.

The 5-year survival for malignant GIST varies widely and has been reported to be from 28 to 80 %. Median survival of patients in whom complete surgical resection is not possible is 10–23 months. The median survival from the time of diagnosis of metastatic or recurrent disease has been reported from 12 to 19 months.

The following are poor prognostic features:

1. Age >50 years
2. Recurrent presentation
3. Size >5 cm
4. Microscopically positive surgical margins
5. Mitotic activity >5 mitoses/hpf
6. Absence of *c-kit*

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