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Emergency Presentation and Management of Gastrointestinal Stromal Tumour: Our Experience

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Abstract
Background: *GIST are the most common mesenchymal tumours of the GI tract and in GI tract it arises most commonly from stomach followed by small intestine. Mostly GIST is asymptomatic and their presentation depends upon their site and size. Symptomatic patients present with anaemia, GI bleeding, abdominal pain and obstruction. Complete resection is standard and curative. Tyrosine kinase receptors are useful in management of high risk GISTs, advanced, recurrent and metastatic tumours.*
Aim: *The aim of this study is to analyse the clinical data of GIST patients who presented with acute symptoms.*
Material and Methods: *The clinical data of GIST patient who presented between Jan 2013 to Mar 2018 along with their clinical presentations, radiological and endoscopic data, surgical procedures, follow up data were collected and analysed.*
Results: *23 patients (13 males and 10 females) presented with acute symptoms who were diagnosed to have GIST. The GIST was located in stomach in 10 patients, in small intestine in 10 patients, in colon in 1 patients and in rectum in 2 patients. Pain abdomen and GI bleeding were the most common symptoms followed by intestinal obstruction. All 23 patients underwent surgical exploration. Complete macroscopic resection was achieved in 21 patients, while 2 patients had palliative and incomplete resection. Two patients with small intestine GIST developed recurrence/ metastases. One patient had mortality on 2 years follow-up.*
Conclusion: *GISTs are uncommon tumours and few of GISTs presents with acute symptoms. The patients with chronic anaemia and recurrent abdominal pain need evaluation and work up for GIST. Surgery remains the gold standard treatment in localized GIST. Large GISTs may require Neo-adjuvant chemotherapy to increase resectability of tumour. Anatomical site of primary tumour, size of tumour, completeness of surgical resection, tumour pseudo capsule rupture and response to chemotherapy affects the prognosis and recurrence. Early resuscitation, diagnosis and surgical treatment affects the outcome in GIST related emergencies.*
Keywords: *Gastrointestinal Stromal Tumours, Imatinib, Tyrosine Kinase Inhibitors, Intussusception*

Introduction

Background: Gastrointestinal stromal tumours (GIST) are most common mesenchymal neoplasms of the gastrointestinal tract. GIST originates from the Interstitial cell of Cajal, considered as *pacemaker* of gastrointestinal motility[1]. GISTs may be found anywhere in the GI tract, however, the most common location is the stomach (56%), followed by the small intestine (32%) and colon and rectum (6%) [2, 3].

On IHC (Immunohistochemistry), most of the GISTs are positive for KIT (CD117) and DOG-1. CD117 (c-kit proto-oncogene product) protein, a tyrosine kinase growth factor receptor, is the most specific and important immunochemical marker for GIST. Few GISTs are CD117 negative, which are PDGFRA-mutated GISTs [4,5,6].

Clinical Features: GISTs are mostly asymptomatic and are discovered only as incidentally for other indications. Symptoms of GIST are related to the size and location of the tumour. Some GIST has acute presentations with gastrointestinal bleeding (Mucosal Ulceration), hemoperitoneum (Rupture or perforation) and intestinal obstructions (Intussusception). But mostly, GISTs are diagnosed because of symptoms of compression from an abdominal mass, chronic anaemia or fatigue. One-fourth of GISTs present and are diagnosed in a clinical emergency, and one-fourth of GISTs are incidentally detected[5]. Early in disease progression, symptoms may be very nonspecific, such as mild pain, bloating, or dyspepsia. Patients presenting with large GISTs may have palpable tumour and present with pressure or pain or other symptoms.

Staging & Risk Stratification: Small GIST of size < 2 cm with low mitotic index (< 5/50 HPF) can be managed conservatively if asymptomatic as they have low malignant potential. However, mitotic index > 5/50 HPF has malignant risk potential[7].

Gastric GISTs are biologically less aggressively than tumours that arise in other locations. Current American Joint Committee on Cancer (AJCC) staging of GISTs includes tumour size, presence of nodal metastasis, distant metastasis, and grade (high grade is > 5 mitoses/50 high-power field)[8].

Table 1: AJCC 8 Staging [8]

Definition of Primary Tumor (T)		
T Category	T X	Primary tumour cannot be assessed
	T 0	No evidence of primary tumour
	T1	Tumour 2 cm or less
	T2	Tumour more than 2 cm but not more than 5 cm
	T3	Tumour more than 5 cm but not more than 10 cm
	T4	Tumour more than 10 cm in greatest dimension
Definition of Regional Lymph Node (N)		
N Category	No	No regional lymph node metastasis or unknown lymph node status
	N1	Regional lymph node metastasis
Definition of Distant Metastasis (M)		
M Category	M0	No distant metastasis
	M I	Distant metastasis
Definition of Mitotic Rate		
	Low	5 or fewer mitoses per 5 mm 2, or per 50 HPF
	High	Over 5 mitoses per 5 mm 2, or per 50 HPF

Various clinicopathological criteria have been developed to assess the malignant potential of GIST like Fletcher criteria[10] and the Joensuu criteria [11]. These criteria included mitotic index, tumour size, tumour location, and tumour rupture.

Table 2: Survival Data & Disease Progression in GIST [9]

Organ	Stage	Tumour Size (cm)	Mitotic Rate	Observed Rate of Progressive Disease
Stomach	Stage IA	< 5	Low	0 -2 %
	Stage IB	> 5 - 10	Low	3 -4 %
	Stage II	< 2	High	Insufficient data
		> 2 - 5	High	16%
		> 10	Low	12%
	Stage IIIA	> 5 – 10	High	55%
	Stage IIIB	> 10	High	86%
Small Bowel	Stage IA	< 5	Low	0-4 %
	Stage II	> 5 -1 0	Low	24 %
	Stage IIIA	>10	Low	52 %
		< 2	High	50 %
	Stage IIIB	> 2 -5	High	73 %
		>5-10	High	85 %
		>10	High	90 %

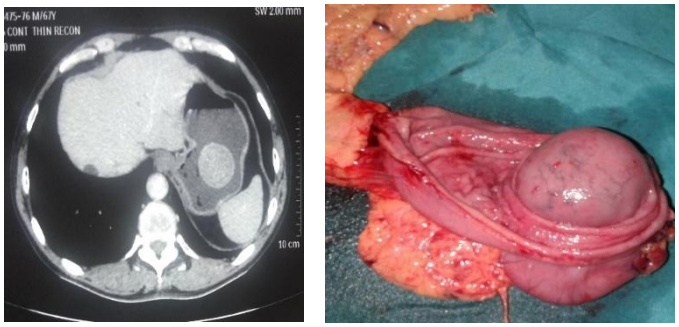
Table 3: Joensuu Modification of GIST Risk Stratification for Adjuvant Chemotherapy [11]

Risk Category	Tumour Size (cm)	Mitotic Index (per 50 HPF)	Primary Site
Very Low Risk	< 2.0	≤ 5	Any
Low Risk	2.1 – 5.0	≤ 5	Any
Intermediate Risk	2.1 – 5.0	> 5	Gastric
	< 5.0	6- 10	Any
	5.1 – 10.0	≤ 5	Gastric
High Risk	Any	Any	Tumour Rupture
	> 10	Any	Any
	Any	> 10	Any
	> 5.0	> 5	Any
	2.1 – 5.0	> 5	Non-Gastric
	5.1 – 10.0	≤ 5	Non-Gastric

Imaging: CECT abdomen is most useful in evaluation, diagnosis and post-operative follow-up of GIST. Findings are variable, depending on the size and aggressiveness of the lesion. Large GISTs often displace adjacent organs and they appear as hyper vascular, enhancing masses with heterogeneous because of necrosis, haemorrhage, or cystic degeneration. Smaller GISTs are usually more homogeneous and polypoid in appearance[12]. CECT is also useful in assessing the effect of neo-adjuvant chemotherapy with Tyrosine kinase inhibitors prior to surgery. The response to chemotherapy is characterized by rapid transition from a heterogeneously hyperattenuating pattern to a homogeneously hypoattenuating pattern with resolution of the enhancing tumour nodules as well as decrease in tumour vessels. Sometimes, tumours size may paradoxically increase during chemotherapy due to intra lesion haemorrhage or myxoid degeneration. However, the tumour enlargement is associated with decrease in tumour enhancement [12].

Endoscopy: Stomach and duodenal GISTs can be detected on Upper GI endoscopy for evaluation of dyspeptic symptoms or hematemesis. The sub-mucosal exophytic growth may not be detected on Upper GI endoscopy. It can be seen as submucosal mass with smooth appearance or as a bulge into the stomach lumen (Figure 1) or as exophytic mass (Figure 2). In patient who presents with bleeding or anaemia, the mass with mucosal ulceration (Figure 3) may be seen. Similarly, Colonoscopy can detect colorectal GIST. Endoscopy can provide tumour tissue for histopathological examination prior to surgery [13].

Figure 1: Stomach, Intraluminal Growth



EUS (Endoscopic Ultrasonography) is useful in detection of very small (<2 cm) gastric and oesophageal GISTs. High risk feature on EUS areirregular borders, cystic spaces, ulceration, echogenic foci, and internal heterogeneity[14].

Figure 2: Stomach, Exophytic Growth

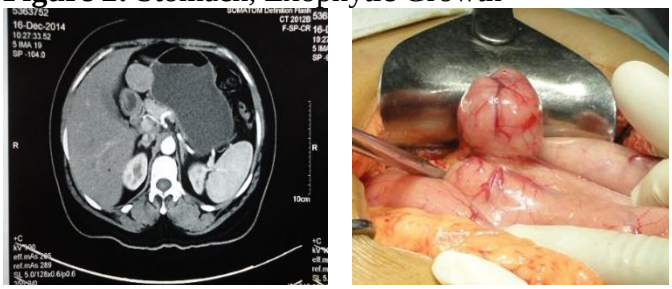


Figure 3: Jejunal GIST with Bleeding Ulcer

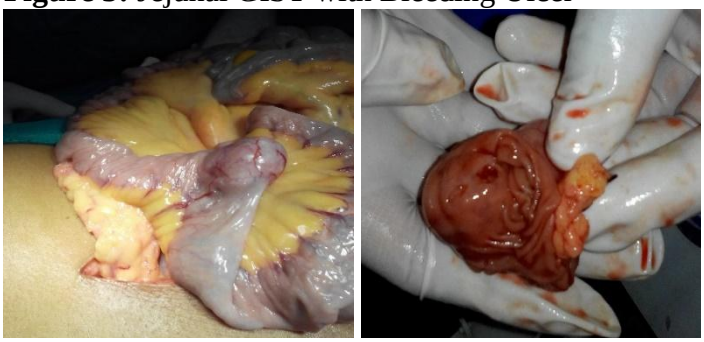
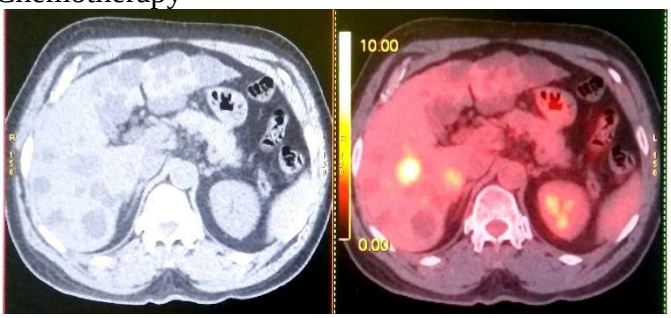


Figure 4: PET-CT Scan with Metastatic GIST on Chemotherapy



PET-Scan: Positron emission tomography (PET) scans is useful in assessing response of chemotherapy (Figure 4). Metabolic response is detected earlier than anatomical changes on PET-CT after neo-adjuvant chemotherapy[15]. Apart from the tumour size, site of origin and mitotic index the Ring-shaped uptake on preoperative PET scan found to be an independent adverse prognostic factor for postoperative recurrence[16].

Management

(a) Surgery: Surgery remains the mainstay of treatment for localised GIST. Small sized GISTs (<

2 cm) with low mitotic index can be observed. However, any small symptomatic GIST (e.g., bleeding from erosions through the mucosa, obstruction) or increase in size on follow-up needs surgical treatment. Aim of treatment is to achieve complete tumour resection with at least a 1- to 2-cm gross margin as well as to preserve maximum organ function. Laparoscopic or laparoscopic assisted resection of tumour can be done. Meta-analysis has found no significant difference in recurrence between laparoscopic or open surgical approach. Although, recovery of patient, intra-operative blood loss and hospital stay are less in laparoscopic approach [17, 18].

Gastric tumour requires partial gastrectomy or gastric wedge resection while jejunal/ileal tumours are managed with segmental resection and anastomosis. Surgery for Colo-rectal GISTs depends on location and size of the lesion, it can range from Low anterior resection or abdominoperineal resection to segmental colon resection [19].

The aim of resection remains R0 excision. The R0 or R1 resection has better prognosis than debulking or macroscopic positive margin (R2 resection). The large tumour size (≥ 10 cm), location (Rectum), and tumour rupture is associated with R1 resection. The difference in recurrence-free survival with or without Imatinib therapy in those undergoing an R1 vs R0 resection was found to be statistically not significant on follow up. Any spillage of tumour, tumour rupture or violation of the tumour pseudo-capsule are risk for tumour seeding and recurrence [20, 21, 22].

(b) Chemotherapy: Imatinib mesylate, and other tyrosine kinase inhibitors, have been used in GIST treatment for chemotherapy (Table 4).Initially,

Table 4: Tyrosine Kinase Inhibitors (TKIs) Used in GIST

TKIs	Doses	Indications
1. Imatinib	400 mg Oral	Daily Standard Dose
	800 mg Daily Oral	Exon 9 KIT-mutated GIST
		Progression on Imatinib 400 mg
2. Sunitinib	50 mg Oral	Daily for 4 weeks every 6 weeks
	37.5 mg Oral	Daily continuously
3 Regorafenib	160 mg Oral	by mouth daily for 3 weeks every 4 weeks

Imatinib was used in metastatic GIST and later it was found to be effective as adjuvant therapy to decrease the recurrence and tumour free survival in high risk cases. It is also used as neo-adjuvant therapy to increase the resectability. [23,24,25]

Aim & Objectives

To analyse the clinical data of patients presenting with acute symptoms who were diagnosed and managed as case of Gastrointestinal Stromal Tumour.

Material & Methods

The study and analysis of data were retrospective and observational. 18 Patients who were admitted between Jan 2013 to Mar 2018 in emergency with acute symptoms were part of retrospective observational study. These patients were evaluated, diagnosed and managed as case of GIST. The patient's data, clinical presentations, blood parameters, radiological and endoscopic findings, tumour morphology, anatomical sites, pathological characteristics, surgical procedures, intraoperative findings and follow-up data were reviewed and analysed.

Results

Total 23 patient included in study, 13 were male and 10 were female patients. The tumours were located in the stomach in 43.47% patients. Anatomical sites and organ of involvement were as in Table 5.

Table 5: Site of Origin

Anatomical Site	Numbers	Percentage
Stomach	10	43.47
Jejunum	5	21.73
Ileum	5	21.73
Rectum	2	8.69
Colon	1	4.34

Four patients presented with acute onset hematemesis or melena. 04 patients were on follow-up for chronic anaemia and presented with acute gastrointestinal bleeding. 05 patients required fluid resuscitation and blood transfusion prior to definitive surgery. 02 patients had intussusception (Figure 5) and presented with intestinal obstruction. Nine patients presented with intestinal colic while 01 patient had bleeding per rectum [Table: 6].

Figure 5: Jejunal GIST with Intussusception

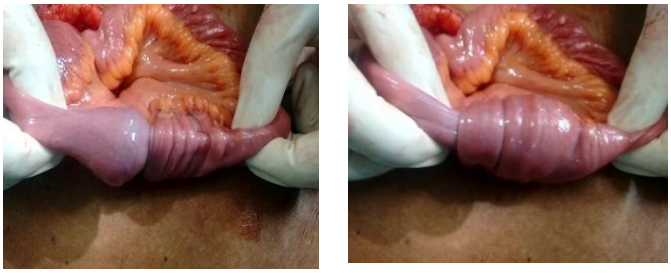


Table 6: Origin of Primary Tumour and Presenting Symptoms

Organ	Symptoms (Multiple)	Numbers
Stomach (n=10)	Dysphagia	2
	Hematemesis	3
	Lump Abdomen	2
	Anaemia	4
	Pain abdomen	3
Ileum/Jejunum (n =10)	Hematemesis / Malena	1
	Chronic Anaemia	1
	Intussusception	2
	Pain Abdomen	6
Colon (n =1)	Pain Abdomen	1
Rectum (n =2)	Bleeding per rectum	1
	Difficulty in Defecation	2
	Bleeding Per Rectum	1

Upper GI endoscopy and biopsy was performed in 16 patients who presented with hematemesis, melena, dyspepsia or gastric outlet obstruction. Colonoscopy was performed in patients presenting with bleeding per rectum.CECT scan of the abdomen & pelvis was performed in all clinically stable patients. Patient with rectal GIST also underwent MRI pelvis to assess the extent of tumour involvement. PET-CT scan was performed in patients with large GIST tumour who were given Neo-adjuvant chemotherapy (Tab Imatinib 400 mg OD). CECT abdomen/pelvis and PET Scan were repeated after Neo-adjuvant chemotherapy to assess the response [Figure 4]. All patients underwent surgery (Table 7). Complete resection was achieved in 21 patients while in 01 patient only diversion ileostomy was performed. One patient who had hepatic metastasis, palliative ileal resection & anastomosis was done to relieve obstruction.

Table 7: Site of Tumour and Surgical Procedures

Site	Procedure	Numbers
Stomach (10)	Gastric Sleeve Resection	5
	Distal/Partial Gastrectomy	4
	Total Gastrectomy	1
Jejunum/Ileum (10)	Resection Anastomosis	9
	Ileal Resection & Ileostomy	1
Colon (1)	Segmental Resection & Anastomosis	1
Rectum (2)	LAR	1
	APR	1

Histopathological examination of preoperative specimen, surgical specimens along with immunohistochemical staining for detection of c-KIT (CD117) was performed. All patients were CD-117 positive. Tumour characteristics and grade were as in Table 8.

Table 8: Grade of GIST and Size of Tumours

Gradeof GIST	Grade	Numbers
	Low Grade (<5/50)	18
	High Grade (>5/50)	5
Size of Tumours	Size	Numbers
	< 2 cm	1
	2-5 cm	8
	5-10 cm	8
	> 10 cm	4
	Multiple Peritoneal Deposits	2

All patients received adjuvant chemotherapy with Tyrosine kinase Inhibitors, however, 05 patients received Neo-adjuvant chemotherapy followed by surgical resection and adjuvant chemotherapy and 02 patient received palliative chemotherapy.

Discussions

Our study included 23 patients (13 Males, 10 Females) with average age of 52.26 years (Range 27-75 years).

Stomach is the most commonly involved organ for GIST (> 50%) followed by small intestine and colon[2,3]. In our study, stomach was affected in >43 % cases.

Most of the GIST remains asymptomatic and are detected incidentally. Some of the GISTs present with acute symptoms like acute pain abdomen, intestinal obstruction, GI bleeding and perforation. Among acute presentations, most common symptoms are GI bleeding (50%), abdominal pain (20-50%) and intestinal obstruction (10-30%) [26]. In our study, pain abdomen and GI bleeding were the most common presentation followed by intestinal

obstruction [Table 6]. Acute GI bleeding patient required resuscitation and blood transfusion before definitive surgery.

Imaging (CECT abdomen/USG abdomen) as well as endoscopy (UGI/Colon) were performed as indicated. In few, PET-CT scan were also done. CECT abdomen was able to detect all lesions. UGI endoscopy was helpful in gastric lesions. After assessing the lesions patient were subjected to surgical resection [Table 7]. In 21 patients, R0 resection was achieved. Five patients required neo-adjuvant chemotherapy followed by surgery. Two patients who presented with intestinal obstruction were found to have metastatic lesions in liver and omentum. They underwent palliative ileal resection.

All tumours were CD-117 positive, most of them were Low grade tumours. Tumour size was 2-5 cm and 5-10 cm in 8 cases each [Table 8]. After histopathology and risk stratification[11], these cases were given adjuvant chemotherapy.

Small bowel GIST has worse outcome than Gastric GIST[27]. On follow up after 2 years, 02 cases of small intestine GIST reported with recurrence of symptoms and lesions. One patient of ileal GIST had mortality due to recurrence and progression on chemotherapy. None of the low-grade small sized tumour and gastric GIST had recurrence on follow up.

Conclusions

GISTs are uncommon tumours and few of GISTs presents with acute symptoms. The patients with chronic anaemia and recurrent abdominal pain need evaluation and work up for GIST. Surgery remains the gold standard treatment in localized GIST. Large GIST may require Neo-adjuvant chemotherapy to increase resectability of tumour. Anatomical site, size of tumour, completeness of surgical resection, tumour pseudo-capsule rupture and response to chemotherapy affects the prognosis and recurrence. Early resuscitation, diagnosis and surgical treatment affects the outcome in GIST related emergencies.

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