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Gastrointestinal Stromal Tumors –A case series –Our Experience Over Four Years in A Tertiary Care Medical College Hospital

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Abstract
Background: *Gastrointestinal stromal tumors (GIST) are mesenchymal tumors and account for 3% of all gastrointestinal malignancies. They are unpredictable, rare, enigmatic and display aggressive behavior[1]. They express tyrosine kinase (KIT) and commonly involve small gut and stomach (rarely esophagus, mesentery and colon). A series of 11 cases of GIST managed in a teaching hospital attached to a medical college over 4 years is presented.*
Methods: *Medical records of the 11 cases of GIST managed during January 2013 through December 2016 were reviewed for patient demographics, clinical presentation, investigation, sites, treatment, histology, immunohistochemistry and Imatinib therapy. Follow up for recurrence over the period ranging from 6 months to 4 years was done.*
Results: *GIST was common in men. Age ranged 28 to 75 years. Sites involved were--small bowel in 5, stomach in 2, mesentery in 2, rectum and greater omentum 1 each. Symptoms ranged from abdominal pain, mass, upper /lower gastrointestinal bleeding, small bowel obstruction. Surgery was the mainstay of the treatment. All were positive for tyrosine kinase. One case was non resectable and another showed metastasis to the mesenteric lymph nodes, which is uncommon. All received Imatinib post operatively. Recurrence was seen in one patient with small bowel GIST at 2 years.*
Conclusions: *GIST are uncommon with varied presentations and may be aggressive and can recur. GIST tumors elaborate tyrosine kinase, hence KIT receptor inhibitor Imatinib was useful in all, nonresectable & recurrent tumors. Tyrosine kinase inhibitor has thus drastically changed the diagnosis and management of these tumors.*
Keywords: *Gastrointestinal Stromal Tumors;Imatinib Mesylate; Tyrosine Kinase.*

Introduction

Gastrointestinal stromal tumor (GIST) are mesenchymal tumors arising from gastrointestinal tract, mesentery, or omentum. They account for upto 3% of gastrointestinal malignancies[1].In frequency these tumors rank distant third after adenocarcinoma and lymphomas of gastrointestinal tract tumors histologically. GIST arise from the interstitial cells of Cajal. These are complex group of cell network which are the pace

makers of the gut and initiate peristalsis[2]. Age incidence for GISTs is usually in adults between 40 and 70 and can be benign or malignant [3]. These tumors most commonly occur in the stomach and the small bowel. Clinical presentation is variable according to the site of tumor and the size. The most common symptoms encountered are abdominal mass, weight loss, gastrointestinal bleeding, anemia, pain abdomen, small or large bowel obstructive symptoms.

GIST rank third in frequency after adenocarcinoma and lymphomas. They form 1-2 % among the histologic types of gastrointestinal tract tumors. 900 new cases are diagnosed in UK every year (figures for India are not available). Expression of tumor marker receptor tyrosine kinase KITby GIST cells has revolutionized the diagnosis and management of GIST during the last 15 years. Discovery of Imatinib Mesylate, a specific tyrosine kinase inhibitor, resulted in significantly improved survival (above 80%). We present a case series of 11 cases of Gastrointestinal Stromal Tumors managed in a tertiary care hospital attached with this medical college, over a period of 4 years (January 2013 through December 2016).

Materials and Methods

This was a retrospective observational study. Medical records of the 11 cases of GIST managed during the period from January 2013 through December 2016 were reviewed for patient demographics, clinical presentation, investigation results (upper gastrointestinal endoscopy and colonoscopy, radiologic imaging). The tumor characteristics-- locations of the tumors, type of surgical resections, histopathology, immunohistochemistry analysis, Imatinib Mesylate therapy post operatively or as palliation (even where resectional surgery not contemplated), treatment outcome were noted and studied. Follow up for recurrence over a period ranging from 6 months to 4 years were also studied. The prognostic factors-- size, mitotic index & metastasis were observed and classified using Fletcher's classification.

Results

Of the 11 patients, men accounted (n=7, 63.7%), women (n=4, 36.3). Age range was 28 to 75 years, mean age 57.7 years, median age 61 years. Symptoms ranged from abdominal pain, epigastric discomfort, mass, upper /lower gastrointestinal bleeding, rectal bleeding, anemia, weight loss and small bowel obstruction. Sites involved were small bowel in (n=5, 45.45%), stomach in (n=2, 18.18%), mesentery in (n= 2, 18.18%), rectum and greater omentum in (n=1, 9.09%) each.

Gastric wedge resection done in 2 cases, small bowel resection anastomosis done in 5 cases, excision of mesenteric GIST with adjacent jejunum in 2 cases. Anterior resection in 1 case of rectal GIST .One (n=1, 9.09%) case of recurrent mesenteric and greater omental GIST was non resectable. One case of mesenteric GIST (n=1, 9.09%) had a resectable tumor but postoperative histopathology reported metastasis to the mesenteric lymph nodes. Recurrence seen in one patient (n=1, 9.09%) with small bowel GIST at 2 years. The non resectable case of recurrent GIST received Imatinib. One case (n=1, 9.09%) received Sunitinib.

The tumor sizes varied from 2.5 cm to 22 cm. Tumor histology showed spindle shaped cells with necrosis and hemorrhage in all cases. Mitotic index varied from 0/50 HPF to >10/10 HPF. One case (n=1, 9.09%) of jejunal mesenteric GIST showed metastatic deposits in 12 out of 24 mesenteric lymph nodes (Intraoperative photograph 1)

Immunohistochemistry (IHC) for CD117/C kit was positive in all cases. Recurrence was seen in one case (n=1, 9.09%) of small bowel GIST at 2 years post treatment. One case (n=1, 9.09%) was lost to follow up and one case died of acute myocardial infarction 7 months post treatment[4] (Table 1).

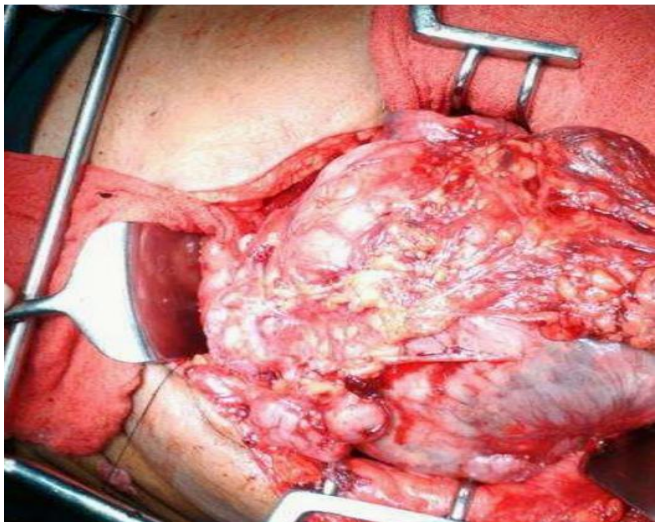
Discussion

GISTs are the commonest mesenchymal tumors of the gastrointestinal tract. Apart from stomach, small gut, they may originate in the large gut,

esophagus, mesentery and omentum. The *American Joint Committee on Cancer (AJCC) Cancer Staging Manual* lists the following approximate distributions--Stomach (60%),Small intestine (30%),Rectum (3%),Colon (1–2%), Esophagus (<1%), Omentum /mesentery (rare)[3]. Infrequently, GIST may arise in the appendix, gallbladder, pancreas, retroperitoneum, and tissues around pelvic organs.

GISTs were found commonly in adult males, between ages 28 – 75 years (40 and 70 years as per published literature[3]) and can be benign or malignant[2]. Presenting complaints depended on the site of the GIST. Small gut GIST presented with small gut obstruction, abdominal lump. Gastric GIST presented with epigastric discomfort, upper gastrointestinal bleeding. Rectal GIST presented with rectal bleeding. Mesenteric /omental GIST reported with abdominal mass, anemia.

The abdominal radiograph (straight, erect) showed features of small /large gut obstruction. Ultrasound, CT scan, MRI showed the site, size of the tumors and the adjacent organs (liver, lymph nodes for involvement). Upper gastrointestinal endoscopy and colonoscopy showed wall irregularity and thickening in gastric and colonic /rectal GIST respectively.



All patients required surgery. One case of greater omental GIST was unresectable as it involved inferior vena cava, aorta, left kidney and left colon.20 to 25% of gastric and 40 to 50% of small gut GIST exhibit aggressive behavior.[5] Metastatic GIST is found in 10% to 25% of patients [5,6]. Oncogenic mutations are detected in 85% of GIST in either KIT or PDGFRA (platelet-derived growth factor receptor alpha) tyrosine kinase receptors.[7] GIST pathogenesis is the result of activation of either of these tyrosine kinase receptors.[7,2] Histologically GIST is composed of the following[8] --- Spindle cells (70%), Epithelioid cells (20%),Mixed spindle and epithelioid cells (10%).[7]

All received Imatinib post operatively. Imatinib Mesylate (IM) is tyrosine kinase receptor inhibitor and is the hallmark of treatment of GISTs. Imatinib has exhibited response rate in >80% cases and enhanced the survival to >5yrs in more than 50% of unresectable or metastatic GISTs. The dosage of Imatinib should be modified in hepatic or renal impairment. Common toxic effects of IM are nausea, vomiting, skin rash, and bone marrow depression and in some patients with tumor hemorrhage has been noted Predictors of aggressive behavior in GISTs have been proposed as --Very low risk—size <2cm, mitotic index <5/50 HPF, low risk- 2-5 cm, mitotic index <5/50 HPF, intermediate risk- <5cm, 6-10 /50 HPF mitotic index or 5-10 cm ,6-10 /50 HPF, high risk- >5cm and >5/50 HPF or >10 cm & any mitotic rate or any size and >10 /50 HPF.

Predictors for recurrence are-- tumor size >5cm, high grade, tumor rupture, small bowel origin[5,8] (From) Every effort should be made to avoid tumor rupture during surgery as this drastically reduces survival[10].A study conducted by Pierie et al and De Matteo showed high recurrence in GIST with high risk features. 5-year survival was 42% when complete resection was done as compared to 9% if the excision was incomplete.[8]

We had used Imatinib in the recurrent unresectable mesenteric and omental GIST and all the operated cases postoperatively. Indications of preoperative Imatinib are: large localized, resectable tumors, impending hemorrhage or rupture, poorly localized small tumors that are difficult to resect, non-metastatic but unresectable

localized GISTs and If tumor free resection margins not achievable. Preoperative Imatinib may be continued until maximal response is achieved.

Response should be assessed after 8 weeks of initiation[4]. In our series one case of recurrence of small bowel GIST and another case of unresectable recurrent mesenteric GIST received Imatinib for 12 weeks and showed good palliation and regression of the tumors.

A very peculiar feature of this series was that in one patient of jejunal mesenteric GIST whose tumor was resected but showed metastasis in the mesenteric lymph nodes (12 out of 24 lymph nodes were positive), a very unusual feature of metastatic GIST.

Sr No.	Age /sex	Location of the GIST	Primary symptom	Size of the tumour	Primary treatment	IHC Analysis	histopathology	Post op treatment (imatinib/sunitinib	FU /recurrence & time period
1	66/ M	Small gut	Small bowel obstruction	10 cms	Surgery	CD117/Ckit positive	Spindle cells 8-10 /HPF	YES	YES,2 yrs post op
2	75/ M	Body of stomach	Upper G I bleeding	5x3.5x3. 5	Surgery	CD117/Ckit positive	Spindle cells <5/50 HPF	YES	No, at 2yrs 7 months
3	42/F	Small gut	Lower abd pain	4.8cms	Surgery	CD117/Ckit positive	Spindle shaped cells,9/50 HPF	YES	No 18 months
4	61/F	Rectum	Lower GI bleeding	8 cms	Surgery	CD117/Ckit positive	Spindle cells 5/50 HPF mitotic index	YES	No, 1 yr post treatment
5	38/ M	Jejunum	Abd pain , rectal bleeding	2.5 cms	Surgery	CD117/Ckit positive	Spindle cells,<1/50 HPF	YES	Lost to follow up
6	80/ M	Stomach	Epigastric discomfort	3 cms	Surgery	CD117/Ckit positive	Severe nuclear atypia,6/50 HPF Mitotic index	YES	No, till 1 yr post treatment, died of ac myocardial infarction
7	38/F	Mesentery	Abd discomfort	20x18x1 6 cms	Surgery	CD117/Ckit positive	Spindle cells,twisted nuclei,7/50HPF	YES	No, 30 months post treatment
8	65/ M	Greater omentum	Abd lump	20x17x6	Surgery	CD117/Ckit positive	Mixed spindle and epitheloid cells,2/50HPF	YES	No, 6 months post treatment
9	28/F	Small gut	Abd pain	13x10x9	Surgery	CD117/Ckit positive	Mixed spindle and epitheloid cells5/50 HPF	YES	No, 3 yrs post treatment
10	70/ M	jejunum	Rt IF ,Rt lumbar,umbilical areas mass	10x8x6 cms	Surgery	CD117/Ckit positive	Spindle cells, 7/50 HPF	YES	No, 4 months post treatment
11	65/ M	Jejunal mesentery	Recurrent Large abd mass	22x20x1 5 cms	Imatinib	CD117/Ckit positive	Spindle cells in whorls,>10/10 HPF mitotic index, malignant GIST,high grade	YES	Metastatic disease,surviving 6 months post treatment

Conclusion

GISTare unpredictable mesenchymal tumors. Common sites are stomach and small gut. Mesenteric and omental GIST are rare. Surgery and Imatinib Mesylate therapy are the options available to the surgeon. Imatinib along with complete en bloc surgical excision with a clear margin and unbreached pseudo capsule is the standard initial management for all localized resectable GISTs &help in improving long term survival. For gastric GIST a wedge resection or resection anastomosis for intestine is adequate. En-bloc resection should be consideredif neighboring structures are involved but are removable.

Neoadjuvant Imatinib can be considered for downsizing of initially unresectable tumor thus allowing adequate subsequent resection with reduced surgical morbidity. Adjuvant Imatinib is indicated in patients at higher risk of recurrence. In metastatic or recurrent GIST, the primary treatment would be Imatinib. Sumatinib can be used for resistant or intolerant cases. A multidisciplinary approach and close collaboration

between a medical oncologist, gastroenterologist, radiologist, oncopathologist and principally the surgeon are mandatory to provide GIST patients with the best available treatment.

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