STUDY OF THE CLINICOPATHOLOGICAL PATTERN OF GASTROINTESTINAL STROMAL TUMOURS

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ABSTRACT

BACKGROUND

Gastrointestinal Stromal Tumours (GIST) are a rare mesenchymal malignancy of the Gastrointestinal (GI) tract. GISTs originate from Interstitial Cells of Cajal, the pacemaker cell of the gut. Over the last decade, GISTs have gone from a surgical obscurity to a tumour of extreme interest not only to surgeons but also to oncologists. Surgical management is the mainstay of therapy. They can be benign or malignant in nature. This study aims to analyse the clinical spectrum and various histomorphological features.

Aims-

1. To study the modes of presentation of Gastrointestinal Stromal Tumour, 2. To study the sites of lesion in Gastrointestinal Stromal Tumour, 3. To analyse the stage of presentation of the cases of GIST presenting in Calicut Medical College, 4. To study the pathology (histopathology and immunohistochemistry) to prognosticate the disease. Settings- Department of General Surgery and Gastrosurgery, Medical College Kozhikode, Sample Size- 44 cases over a period of 2 years, Study Period- Jan 2011-December 2012 (2 years), Design of Study- Descriptive Study, Design- Case Control Study.

MATERIALS AND METHODS

Detailed history was taken with regard to the age, sex, mode of presentation, site of lesion, pathology (histopathology and immunohistochemistry). Relevant investigations like CBC, RBS, RFT, LFT, SE, PT-INR, USG abdomen, CECT abdomen, histopathology of specimen including the size and the number of mitosis per high power field and study of immunohistochemistry CD117, performed. The operative findings including tumour size and location and postoperative complications were studied for comparative analysis. Statistical Analysis- SPSS 16.

RESULTS

1. Predominant male affection with a ratio of 1.4:1;
2. Patients presented predominantly with gastrointestinal haemorrhage, i.e. hematemesis and melaena was found in 65% patients;
3. In this study the most common site was found to be stomach 63.6%, followed by small bowel which comprises 25% and colon comprising 4.5%;
4. No specific risk factors with statistical significance could be identified among the cases in the study;
5. In about 25% cases in the study, the average tumour size was more than 10 cms;
6. 63.5% cases of GIST presented with spindle cell morphology and 25% epithelioid morphology;
7. 43 out of 44 cases (97.7%) were positive for CD117.

CONCLUSION

1. GIST can occur anywhere along the GI tract, from oesophagus to the rectum; 2. Of the 44 cases studied during the period 2011 – 2012, there were 26 males and 18 females with a male-to-female ratio of 1.4: 1; 3. The median age group is 60 - 70 years; 4. The predominant site was stomach, 63.6% cases. Gastrointestinal haemorrhage is the most common mode of presentation; 5. Size of tumour and mitotic rate were consistent with malignant behaviour of tumour.

KEYWORDS

GIST, Pathology, CD117, Morphology.

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BACKGROUND

Gastrointestinal Stromal Tumours (GISTs) account for less than 1% of gastrointestinal tumours, but they are the most common mesenchymal tumours of the gastrointestinal tract. GISTs are the third most common neoplasm after adenocarcinomas and lymphomas among gastrointestinal tumours. Previously, these lesions were classified as leiomyomas or leiomyosarcomas because of the presence of smooth muscle features on examination under light microscopy. Later with the advent of electron microscopy, little evidence of smooth muscle origin was shown in these tumours. Immuno-histochemistry in the 1980's

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demonstrated that some of these tumours lacked features of smooth muscle differentiation, while some had markers of neuronal differentiation. The actual cell of origin of GISTs is a pleuripotent mesenchymal stem cell programmed to differentiate into the Interstitial cell of Cajal.[1] These are GI pacemaker cells found in the muscularis propria and around the myenteric plexus and are largely responsible for initiating and coordinating GI motility.

Interstitial cells of Cajal express KIT and are developmentally dependent on stem cell factor, which is regulated through KIT kinase. Immunohistochemical staining for several markers including KIT, CD34, ACAT2, S100, DES and keratin can be helpful in establishing a diagnosis, although KIT positivity is the classic finding for GISTs and is present in 95% of cases.[2,3] 2-5% of tumours are negative for CD117. But the most instrumental development that distinguished GISTs as a unique clinical entity was the discovery of C-KIT proto-oncogene mutations in these tumours. These advances led to the classification of GISTs as a separate entity from smooth muscle tumours, helped illustrate their aetiology and pathogenesis at a molecular level and led to the development of molecular-targeted therapy for this disease.

GISTs can occur anywhere in the gastrointestinal tract. They are submucosal lesions, initially the GIST is contained within the wall (intramural), but as it grows larger it usually extends outward into the abdominal cavity (exophytic). Occasionally, a GIST may grow into the hollow tube of the digestive tract (endophytic). Frequently, GISTs ulcerate the lining at their point of origin and cause bleeding into the GI tract. This blood loss can cause anaemia, but can also be the symptom that brings the GIST to the attention of the patient.

Outcomes in patients with GISTs depends on the clinical presentation and the histopathological features of the tumour. The overall 5-year survival rate ranges from 28-60%. The median survival rate in the localised form of GIST is 5 years, while the median survival rate in the metastatic cases is approximately 10 - 20 months. Larger GISTs are associated with complications such as GI haemorrhage, GI obstruction and bowel perforation.

Clinical presentation provides the most overt evidence for distinguishing benign from malignant behaviour. The morphologic features that appear to be the most predictive of outcome and biological behaviour are tumour size and the mitotic rate. Tumours can be classified into high and low-risk categories based on size, location and mitotic activity.

Approximately, 5000 new GIST cases are expected in the United States annually.[4] The mean age at diagnosis for patients who have GISTs is 63 years with a slightly higher risk in men, especially African-American men.[5] Most commonly GISTs occur in the stomach (50%), small bowel (25%) and colorectum (10%).[5,6,7] At the time of presentation, as many as half of the patients who have a GIST have distant metastases.[7] Of patients who have metastatic disease, nearly two-thirds have hepatic involvement. Isolated hepatic metastatic disease is common in patients with hepatic involvement. Extra-abdominal metastases and lymph node metastases at presentation are rare.[7] The most common symptoms associated with GISTs are vague, nonspecific abdominal pain or discomfort. Patients also presented with a history of early satiety or a sensation of abdominal fullness. Rarely, an abdominal mass is palpable. GISTs may also produce symptoms secondary to obstruction or haemorrhage.

The most favourable subset for disease outcomes seems to be patients who have completely resected localised disease. Even in the setting of complete resection; however, recurrence is relatively common. Patients in whom complete resection is possible and no targeted adjuvant therapy is delivered, approximately 40% experience a recurrence.[7] Isolated local recurrences account for one-third of these recurrences, and distant metastases alone account for nearly half of these recurrences. Positive resection margins are associated with a higher risk for local recurrence. A more malignant phenotype of GIST has been described to occur in approximately 30% of cases,[8] characterised by a high risk for local recurrence, peritoneal spread and development of hepatic metastasis.[9]

Risk	Size (cm)	Mitosis per HPF
Very Low	< 2	< 5
Low	2 - 5	< 5
Intermediate	< 5 5 - 10	6 – 10 < 5
High	>5 > 10 Any size	>5 Any > 10

Table 1. NIH or Fletcher Risk

MATERIALS AND METHODS

The present descriptive study included 44 histologically proven cases of GIST who were operated from Dept. of General Surgery and Gastrointestinal Surgery. Detailed history was taken with regard to the age, sex, mode of presentation. Site of lesion, pathology (histopathology and immunohistochemistry) was studied. Relevant investigations like CBC, RBS, RFT, LFT ,SE, PT-INR, USG abdomen, CECT abdomen, histopathology of specimen including the size and the number of mitosis per high power field and study of immunohistochemistry CD117 were performed. The operative findings including tumour size and location and postoperative complication were studied for comparative analysis.

RESULTS

A total number of 44 cases of Gastrointestinal stromal tumours reported in last 2 years (2011 - 2012) were included

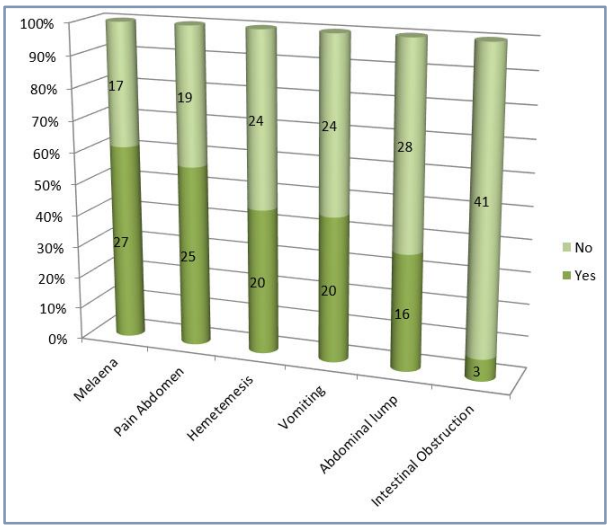
in this study. The age of the patients ranged from 24 to 80 years. The mean age was found to be 55.4 ± 12.85 years. The median age group is 60 - 70 years.

Age (Years)	Frequency	Percent
20 - 30	1	2.3
30 - 40	3	6.8
40 - 50	10	22.7
50 - 60	8	18.2
60 - 70	16	36.4
70 - 80	5	11.4
80 - 90	1	2.3
Total	**44**	**100.0**

Table. 2 Incidence

Gender	Frequency	Percent
Female	18	40.9
Male	26	59.1
Total	**44**	**100.0**

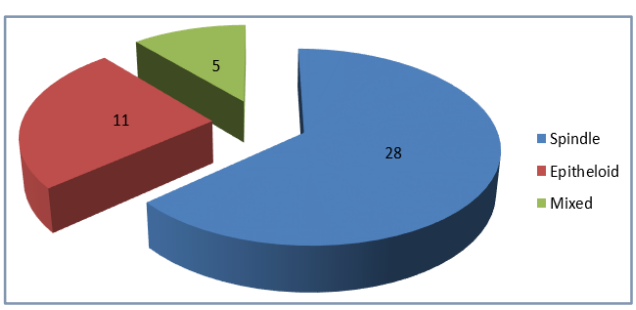
Table 3. Sex Distribution

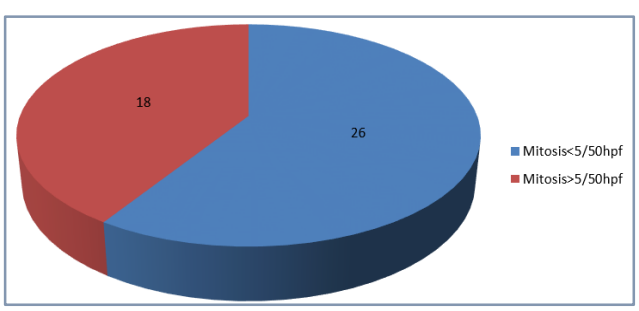


Graph 1. Mode of Presentation

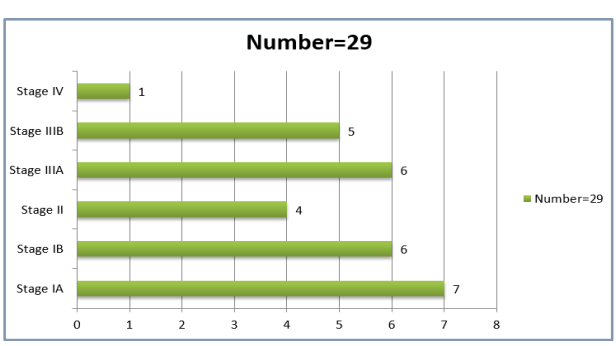
T Stage	Frequency
1.00	1
2.00	13
3.00	19
4.00	11
Total	**44**

Table 4. Tumour Size

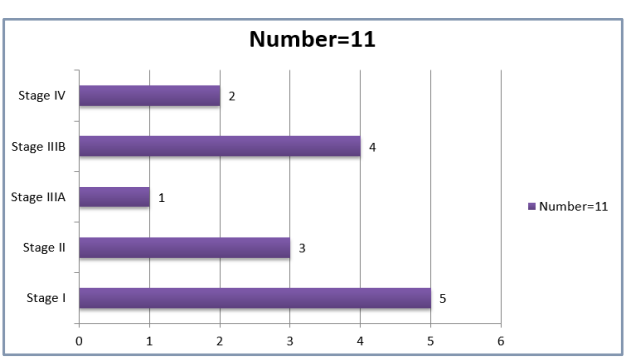




Graph 2. Histopathology



Graph 3. Staging Gastric GIST



Graph 4. Small Intestinal GIST

DISCUSSION

The age distribution in our study shows the most common affection in the fifth and sixth decades of life with mean age being 55 years. This series shows a predominant male affection with a ratio of 1.4:1 for males: females. Literature review shows the mean age to be around 63 years with a slight male preponderance.[5]

Nearly, all the patients presented predominantly with gastrointestinal haemorrhage, i.e. haematemesis and melaena was found in 65% patients. All cases were operated electively, while 6% of them presented as intestinal obstruction requiring emergency laparotomy.

In this study, the most common site is stomach 63.6% followed by small bowel which comprises 25% and colon comprising 4.5%. This in comparison with the statistics in general (eg- De Matteo et al) where stomach comprised 50%, small bowel 25% and colorectum 10%.[7,10] Small bowel GIST showed equal occurrence in age groups below and above 50, whereas gastric GISTs were more common in age group above 50 years.

Symptoms usually depend on the tumour size and location. Most common symptom is gastrointestinal haemorrhage in the form of haematemesis or melaena or both.[10]Pain abdomen is found to be present in 56.8% cases in our study. Two patients presented with intestinal obstruction, whereas 1 patient presented as colonic perforation and foecal peritonitis requiring emergency surgery. No specific risk factors with statistical significance could be identified among the cases in the study. Loss of weight and loss of appetite were present in 4 and 5 patients respectively; 17 patients had pallor and their haemoglobin reached as low as 2.9 requiring multiple blood transfusions in the severely anaemic ones.

In about 25% of the cases in the study, the average tumour size was more than 10 cms. These large-sized tumours had bad prognostic features like high mitotic rate. One patient presented with hepatic metastasis.

Of 28 cases of Gastric GIST 19 were treated by sleeve resection, 6 were treated by subtotal gastrectomy and Billroth II anastomosis and 3 were treated by total gastrectomy and Roux-en-Y anastomosis. Small bowel GISTS were treated by wide excision and end-to-end anastomosis, whereas for 1 case of GIST arising from duodenum 2nd part, Whipple's procedure was done. One patient presented with recurrence twice after surgery. One patient presented with hepatic metastasis after previous surgery for GIST.

In our study, 63.5% cases of GIST presented with spindle cell morphology and 25% epithelioid morphology which is in comparison with the known studies where spindle cell morphology accounts for 70% of the cases and epithelioid 20% cases.[2]

43 out of 44 cases (97.7%) were positive for CD117, which is in comparison with the observations of previous literature.[2,3] Though perfect separation of benign and malignant GISTs could not be achieved, we could predict the prognosis using various grading systems. The main prognostic factor identified was mitotic count and tumour size. Other parameters proposed to affect the outcome are high cellularity, mixed cell type, nuclear grade, vascularity, necrosis and mucosal ulcerations.

Surgical management is the mainstay of therapy with margin-negative resection being the optimal surgical outcome.[11] Targeted therapy with tyrosine kinase inhibitors has revolutionised the care of these patients, providing improved outcomes for patients who have completely resected tumours and resulting in prolonged responses in patients who have advanced disease. With ongoing advancements in the field, it is possible that targeted therapy may be selected in the future based on the specific mutation exhibited in each GIST and the resulting expected response rates. Newer tyrosine kinase inhibitors and targeted agents are being developed with the hope of providing improved response rates or alternative therapies for patients progressing on established agents.[12]

CONCLUSION

- GIST is a rare tumour with a complex natural history.
- GIST can occur anywhere along the GI tract, from oesophagus to the rectum.
- Of 44 cases studied during the period 2011 – 2012, there were 26 males and 18 females with a male-to-female ratio of 1.4: 1. The median age group is 60 - 70 years.
- The predominant site was stomach, 63.6% cases.
- Gastrointestinal haemorrhage is the most common mode of presentation.
- Size of tumour and mitotic rate were consistent with malignant behaviour of tumour.

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