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GIST: A Retrospective Analysis to Define Epidemiology, Clinical Presentation And Diagnostic Modality Used in the Management.

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Abstract: *Gastrointestinal stromal tumors (GISTs) are uncommon mesenchymal tumors arise from the interstitial cells of Cajal, the pacemaker cells of the GI tract.This study was designed to analyze the epidemiology, mode of presentation, the site and investigations for GIST.*
Methods : 54 patients from Kasturba Hospital Manipal that were diagnosed to have GIST from January 2004 to December 2013 were retrospectively studied from their medical records. The data collected focused on the clinicopathological features,the relevant investigations and treatment.
Results: The majority of patients are male and disease is common in old age. Patients most frequently presented with abdominal pain irrespective of the site of the tumor. Stomach is the commonest site of tumor and CECT scan done for 32 patients confirmed the widespread of occurrence of GISTs in the stomach. Immunohistochemistry for cKIT was positive in 100% patients.
Conclusion: GIST is most common in age group 51-60 years, with male predilection. Stomach is the commonest location for a primary tumor, followed by the small bowel with symptoms of abdominal pain, mass per abdomen and gastrointestinal bleeding. CECT is the investigation of choice. Histopathology and immunohistochemistry are more reliable for the diagnosis; IHC reveals that c-KIT mutations are frequently present.
Key-words*: c-KIT,GIST, Immunohistochemistry, Mesenchymal, Pacemaker*

I. Introduction

Gastrointestinal stromal tumors are rare sarcomas of the gastrointestinal tract (GIT) with an incidence of 10-20/million per year[1]. These tumors are found anywhere in the gastrointestinal tract, most commonly in the stomach and small intestine [2-6] and are comprised of spindle cells and epitheloid or pleomorphic mesenchymal cells [2]. GISTs originate from the interstitial cells of Cajal which are located in the submucosal and myentric plexuses of the GIT. GISTs are known to occur due to mutations present most commonly in the KIT gene; this mutation enables uncontrolled activation of tyrosine kinase which is responsible for cell mitosis and thus cellular proliferation [7]. Less commonly mutations are found in the PDGFRA gene [8].

Patients are generally over the age of 50 [2].Common symptoms include vague abdominal discomfort, chronic bleeding in the form of hematemesis or melena while some patients are asymptomatic [3, 4]. Contrast enhanced computed tomography (CECT)scan is the investigation of choice as it gives extensive and valuable information about the growth and its spread [6, 9, 10]. It is recommended to obtain a tissue sample through an endoscopic ultrasound-guided fine needle aspiration (EUS-FNA) prior to beginning tyrosine kinase inhibitor therapy, but is not required before surgical intervention [6, 9, 11-14]. The treatment of choice for GIST is complete surgical resection of the tumor provided that it is localized and not advanced; in case of advanced tumors and mestatic disease tyrosine kinase inhibitors such as Imatinib Mesylate are used [6, 9, 15].

II. Materials And Methods

The medical records of all the patients diagnosed with GIST from January 2004 to December 2013 at Kasturba Hospital Manipal were collected and retrospectively reviewed. A total of 54 cases of GIST were diagnosed within the period of 10 years and were all included in the study. All of the medical records were chosen because the histopathology reports confirmed GIST as the final diagnosis. The histopathology reports were prepared by staff working at the pathology department of Kasturba Medical College Manipal. The information obtained from the records included the patient's age, sex, mode of presentation, and the location of tumor. The location of the tumor was defined by combining the operative and histopathology reports from each medical record.

In addition the relevant investigations that led to the diagnosis of GIST including X-rays, upper and lower gastrointestinal endoscopy, abdominal ultrasound, CECT scan and histopathology reports were reviewed.

III. Results

There were 54 cases that were reviewed retrospectively at Kasturba Hospital and were categorized into patient characteristics, tumor site, clinical presentation, and investigations.

Patient Characteristics

Of the 54 patients 37 patients were male, suggesting a male preponderance. In this study, the youngest patient was 23 years old and the eldest was 82. The most common age group affected was between 51-60 years; 18 out of the 54 fell into that category.

In each of the 41-50 years, 61-70 years, and above 70 years age groups there were 9 cases of GIST. Between the 31-40 years age group there were 8 patients and there was 1 patient that was below 30 years. This data is given in Table 1.

Table 1. Patient Characteristics

	Number of Patients	**Percentage**
Gender		
Male	37	68.5
Female	17	31.5
Age		
< 30 years	1	1
31-40 years	8	15
41-50 years	9	17
51-60 years	18	33
61-70 years	9	17
>70 years	9	17

Tumor Site

The most common site of origin for GIST in this study was the stomach, followed by the small intestine. In 31 patients GIST was diagnosed in the stomach, while 13 GISTs were found in the small intestine. Of those 13, 6 were in the jejunum, 3 in the duodenum, and 4 in the ileum. Large intestinal GISTs were found in 4 patients; 2 in the colon and 2 in the rectum. Extraintestinal GISTs were found in 6 cases; 1 in the pancreas, 2 in the lesser sac, and 3 in the retroperitoneum.

Table 2. Tumor Site

	Number of Patients	**Percentage**
Stomach	**31**	**57**
Small Intestine	**13**	**24**
Jejunum	6	11
Duodenum	3	5
Ileum	4	8
Large Intestine	**4**	**8**
Colon	2	4
Rectum	2	4
Extraintestinal	**6**	**11**
Pancreas	1	2
Lesser Sac	2	4
Retroperitoneum	3	5

Clinical Presentation

Depending on the site of origin the presentation of the tumor differed. Patients with stomach GIST primarily presented with complaints of vague abdominal pain,23 patients presented with this complaint. In the remaining patients 10 came with complaints of mass per abdomen, 9 with loss of weight and loss of appetite, 6 with GI bleeding, and 3 with vomiting. Of the 14 cases with small intestinal GIST, 7 came with vague abdominal pain, 5 presented with mass per abdomen, 3 had loss of weight and appetite, 2 had GI bleeding and 1 presented with acute abdomen due to perforation of a jejunal GIST. Of the 2 colonic GIST patients 1 presented with chronic abdominal pain and lower GI bleeding and the other had abdominal pain along with anemia. Of the 2 rectal GIST patients, 1 came with obstruction and a palpable rectal mass while the other came with a palpable rectal mass and bleeding per rectum. The 1 pancreatic GIST patient presented with jaundice and pruritus and the 5 patients with lesser sac and retroperitoneal tumors complained of both abdominal pain and mass per abdomen. The results for the clinical presentation of various tumors are summarized in Table 3.

Table 3. Clinical Presentation

	Number of Patients	**Percentage**
Stomach		
Vague Abdominal pain	23	74
Mass per abdomen	10	32
Loss of weight and appetite	9	29
GI Bleeding	6	19
Vomiting	3	10
Asymptomatic	2	7
Small Intestine		
Vague Abdominal Pain	7	54
Mass per abdomen	5	39
Loss of weight and appetite	3	23
GI bleeding	2	15
Acute abdomen	1	11
Colon		
Abdominal pain and lower GI bleed	1	50
Abdominal pain and anemia	1	50
Rectum		
Obstruction and palpable rectal mass	1	50
Bleeding P/R and palpable rectal mass	1	50
Extraintestinal		
Abdominal pain and mass per abdomen	5	83
Jaundice and pruritus	1	17

In this study, patients underwent a variety of investigative procedures such as endoscopy, ultrasound, x-ray, and CECT scan. Of the 54 patients 34 underwent endoscopy in which a growth was visualized in 28 patients. Abdominal radiographs were taken for 4 patients out of which 1 showed evidence of pneumoperitoneum and 3 showed features of intestinal obstruction. Abdominal ultrasound was done for 36 patients; it exhibited the location of the tumor. In 26 patients the tumor was found in the stomach with thickening of the stomach wall. There were 5 in the small intestine; 3 were difficult to visualize due to gaseous distension and 2 had a poorly demarcated mass. There was 1 tumor was in the large intestine and it was characterized by thickening of the colonic wall. Extraintestinal GIST was observed in 4 patients and 2 had metastasized to the liver from the stomach and the pancreas. No patients were found to have features of ascites.

	Number of Patients	**Percentage**
Gastroscopy/Colonoscopy		
Growth Visualized	28	82
No Growth	6	18
Ultrasound abdomen		
Stomach	26	72
Small Intestine	5	14
Large Intestine	1	3
Extraintestinal	4	11
Liver Metastasis	2	6

CECT was performed for 32 patients. Of these 16 had tumors in the stomach, 7 in the small intestine, 4 in the large intestine (2 in the colon and 2 in the rectum), and 5 outside the intestine. Of the 32 cases, 13 were intraluminal and 19 were extraluminal. There were 10 tumors which were less than 5 cm in size, 14 were between 5 and 10 cm, and 8 were larger than 10 cm. Round contours were observed in 14 cases and lobulated in 18 cases. Evidence of cystic necrosis and heterogeneous enhancement was found in 31 patients. Only 3 CECT reports established the presence of metastasis. There was no evidence of tumor calcification in any of the GISTs and no significant lymphadenopathy was observed according to the CECT results.

	Number of Patients	**Percentage**
Site		
Stomach	16	50
Small Intestine	7	22
Large Intestine	4	12.5
Extraintestinal	5	15.6
Size		
< 5 cm	10	31
5 – 10 cm	14	44
>10 cm	8	25
Contours		

Round	14	44
Lobulated	18	56
Location		
Intraluminal	13	41
Extraluminal	19	59
Metastasis		
Present	3	9
Absent	29	91

Histopathological specimen was acquired post-operatively/ pre op biopsy. Spindle cells were present in 28 specimens, epithelioid cells in 19 specimens, and mixed histology in 7 specimens. Based on the tumor size and the mitotic index, the tumors were classified into various risk strata. There were 10 low risk tumours, 14 intermediate risktumours, and 30 high risktumours. The specimens were also sent for immunohistochemistry (IHC). All 54 cases were found to be cKIT positive; 14 cases showed CD34, 5 cases showed S100, and 6 cases showed SMA positivity.

	Number of Patients	**Percentage**
Histopathology		
Spindle Cells	28	52
Epitheloid cells	19	35
Mixed	7	13
Risk Stratification		
Low	10	19
Intermediate	14	26
High	30	55
Immunohistochemistry		
cKIT	54	100
CD 34	14	26
S 100	5	9
SMA	6	11

IV. Discussion

Gastrointestinal stromal tumours are rare, representing 0.2% of gastrointestinal tract malignancies (**1).**Due to the uncommon occurrence, non-specific clinical presentation and difficulty to obtain a pre-operative diagnostic biopsy these tumors are challenging to diagnose. There has been recent emergence of knowledge that reveals that activated KIT tyrosine kinase is responsible for the growth of GIST andit has led to the discovery of imatinib mesylate for targeted therapy (**16, 17**). These advances in the understanding of GIST and its management substantiate the need for an accurate and early diagnosis in order to achieve optimal treatment.

Age And Gender Data:

The most common age group in our case series was 51-60 years (33%). The youngest patient in our study was a 23 year old male, who was the only patient aged less than 30 years. The oldest patient was an 83 year old male. The most common age group in our study was a slightly younger population compared with other studies that reported the mean age in the range of 60-70 years(18-21).

There were more male patients diagnosed with GIST (68.5%) compared with females (31.5%) in our study population.The prevalence in males has also been reflected in recent published literature (16,19,20,22).

Presentation:

Presentation of GISTs are varied. Symptoms and signs are said to be related to the location of the tumor as opposed to the disease itself. Presentation of GIST includes upper or lower gastrointestinal bleeding, abdominal pain or discomfort, anemia, intestinal obstruction, mass per abdomen or rectum, loss of weight, loss of appetite, vomiting, and early satiety (**17**). Some site specific symptoms are dysphagia for esophageal GIST, biliary obstruction for GIST at ampulla of Vater and intussusception for GIST in the small bowel (3,4). Upper and lower GI bleeding may be caused by erosion of the gastrointestinal mucosal walls by the tumor and is seen more often in chronic cases (17**)**. In cases of perforated bowel due to the GIST, bleeding into the peritoneal cavity may cause acute abdominal pain and present as an acute emergency; this was seen in one patient with a jejunal GIST in our study (17**)**. In our study the most common clinical presentation was abdominal pain for GIST in the stomach, small intestine and colon. Vomiting was a complaint in only 3 patients all of which had a GIST in the stomach. Only one patient in our study presented with anaemia and they were diagnosed with GIST of the colon. The single case of pancreatic GIST presented with jaundice and pruritis. Overall the common presentations of GIST irrespective of the site were upper and lower GI bleeding, abdominal pain and palpable mass; these complaints have also been reported to be the most common by other studies (17,**23)**.

Location

As the name suggests, gastrointestinal stromal tumors can arise anywhere along the gastrointestinal tract. In our series the most common location for GISTs was the stomach (57%), followed by the small intestine (24%). There were only 2 cases of GIST in the colon and rectum each. Extraintestinal GIST was diagnosed in 6 patients in our study, 1 in the pancreas, 2 in the lesser sac and 3 in the retroperitoneum. There were no patients that were diagnosed with a GIST in the esophagus in our institution during the study period. Other literature has also observed that the stomach is the most common location for GISTs, closely followed by the small intestine (17-20**).**

Investigations

Imaging modalities that are used to facilitate the diagnosis of GIST include contrast enhanced computed tomography (CECT) scan, endoscopy and ultrasonography (USG) **(24).** In our series the patients underwent a combination of endoscopy, abdominal ultrasonography, x-ray, and CECT scan. Our patients did not undergo endoscopic ultrasonography. The histopathology reports collected were from the post-operative specimens.

Abdominal ultrasound was performed in 36 patients as a non-invasive procedure to detect the presence of any growth along the gastrointestinal tract, metastasis and ascites. In the patients who had GIST of the stomach, presence of a gastric mass was discovered and in some patientsgastric wall thickening was also observed. The case of colonic GIST also showed evidence of wall thickening. Abdominal ultrasound detected a mass in 2 cases of intestinal GIST, however the exact delineation could not be appreciated. According to literature, GISTs may be identified as large heterogeneous tumors, commonly presenting with evidence of necrosis on abdominal ultrasound (25).

Recent literature has varied opinions regarding the necessity in acquiring a preoperative histological diagnosis. Most are of the opinion that a preoperative biopsy is not mandatory in all patients, however a histological diagnosis is required when planning neo-adjuvant therapy and in metastatic disease where surgery is not the desired treatment**(2,17).** Endoscopic ultrasound is used as the tool for obtaining a biopsy preoperatively if required. The sample is obtained either through endoscopic ultrasound-guided fine needle aspiration (EUS-FNA) or by endoscopic ultrasound-guided trucut biopsy. However the use of endoscopic ultrasound for preoperative diagnosis has only been successful in 20-30% of patients (26**).**

GIST can be visualized in patients by performing an endoscopy; depending on the location either an upper or lower endoscopy can be performed. The GIST on endoscopy appears as a submucosal growth with either an intact or ulcerated mucosal surface **(23, 27).** Out of the 34 patients from our study that had undergone endoscopy, 28 patients had a visible lesion while in the remaining 6 patients no growth was identified.

CT scan is the investigation of choice for GIST (17, 28- 30**).**In our study it was used to assess the tumor with respect to its size, contour, extent of invasion into surrounding tissue, intraluminal or extraluminal extension, presence or absence of necrosis and calcification, and finally to assess for metastatic disease. Features in favor of GIST as a diagnosis include a tumor that is rounded to oval, circumscribed mural or extramural non mucosa-based of any size that is seen involving or associated with the esophagus, stomach, or intestine **(26).**
From our CECT reports, the following observations were noted.

Of the 32 cases who underwent a CECT scan, there were 10 cases (31%) of GIST that had a tumor size that was less than 5cm, 14 cases (44%) between 5-10cm, and 8 cases with a tumor more than 10cm in size.The study published by Dematteo (31) reports that more than 2/3^{rds} of the GIST patients in their study had a tumor size of more than 5cm. It appears that GISTs are more often found to be larger than 5cm (17, 31, 32**)** whichmay be attributed to the non-specific presentation of GIST and hence may lead to a delay in the diagnosis.
GISTs are rounded and well circumscribed tumors (2, 25, 26**).** However in our series there were moreGISTs (56%) with a lobulated contour than there were with a rounded contour (44%).

There were 31 GISTs (97%) with heterogenous enhancement that showed evidence of cystic and necrotic changes. Cystic changes are more often demonstrated radiologically when the GIST obtains a large size (25, 26**)**. According to **King et al** on CECT GISTs are typically seen as homogenous enhancements 25). However in our reports, 97% of those who underwent CECT showed the GIST as a heterogenous enhancement; similarly **Rammohan et al**also describedthe tumour as a heterogenous enhancement (17). The varying appearance of GIST on CECT scan makes it difficult to diagnose, therefore necessitating histopathological evaluation for confirmation.

Metastasis was detected by CECTin 3 of the patients (9%) who underwent the scan in our study. All 3 patients diagnosed had metastasis to the liver. Metastatic disease is first diagnosed in about 15-30% of patients according to literature (2, 24**)**, and most frequently spreads to the liver and peritoneum (17, 24, 31, 33, 34)

GIST may be classified into 8 histological types, but more commonly the tumors are composed of spindle cells, epithelioid cells, or pleomorphic mesenchymal cells (2). The majority of the specimens in our

study (52%) contained spindle cells; the rest were comprised of either epithelioid cells or a combination of spindle and epithelioid cells. A previous study conducted on 12 patients also provides information to suggest that GISTs are primarily composed of spindle cells (35). Another study elaborates on the histology of GIST with regards to its location; GISTs in the stomach typically show epithelioid cells on histological evaluation, whereas intestinal GISTs primarily show a spindled morphology (2).

In their 1998 study, Hirota et al reported that c- KIT mutations played a crucial role in the pathogenesis of GIST. On IHC CD117 is the marker for the c-KIT gene(17). While Hirota et al stressed on the importance of c –Kit, it is important to note that the lack of such mutations does not eliminate the diagnosis of GIST (4-6, 36, 37). In our study, 100% of tumors were positive for c-KIT mutations, 26 % were positive for CD 34, 11% were positive for SMA, and 9% were positive for S100. A similar retrospective study done on 43 patients had the following immunohistochemical results: 86% had CD 117, 51.2% had CD 34, and 0 patients had S100 mutations (23). This suggests that CD117 is the most reliable marker for GIST.

Treatment

40**).** The aims in the surgical management of GISTs are to resect the tumour while ensuring the resection of negative margins. It is also imperative to handle the tumour with care intra-operatively to avoid rupture and dissemination of the tumour cells. Lastly intraoperative staging should be performed to rule out any evidence of metastatic disease (17, 41**).**

In our series 47 patients underwent surgery. From the remaining patients, 3 patients were discharged against medical advice, one was not willing to undergo surgery due to financial constraints, and 3 patient were not medically fit for surgery due to high intraoperative risk factors hence were not willing for surgery.

The following complications were observed in the post-operative period (1 month) for the 47 cases that underwent surgery. There were wound infections in 5 cases (11%) all of which were managed conservatively and improved over the course of treatment. One patient had pneumonia post-operatively and was managed conservatively. Another patient developed sepsis due to an anastomotic leak and theyeventually died. Biliary peritonitis developed in one patient for whom re-explorotomy was conducted. Three patients developed subacute intestinal obstruction and were all managed conservatively.

Imatinib

Imatinib mesylate is a tyrosine kinase inhibitor (17**).** It interferes with the substrate phosphorylation and signalling and therefore inhibits the gastrointestinal stromal tumor cells from proliferating and surviving (6, 9, 42**)**.

Imatinib is recommended to be given to patients that have an unresectable tumor, metastatic disease and in those who have high risk GIST (16, 26, 43**).** Imatinib therapy has been found to be beneficial when administered post-operatively **(15, 44-47)**. According to **Rammohan et al** it has shown to improve progression free survival and overall survival if post-operative patients are given Imatinib 36 months following surgery. Imatinib is particularly beneficial in intermediate and high risk patients who did not receive any prior treatment with the same (17**).**

In our study there were 44 patients that had either intermediate or high risk category of GIST. Out of this group of patients 6 were unwilling to receive imatinib therapy. The remaining 38 patients received Imatinib;of these patients, 3 were administered Imatinib pre-operatively as they were diagnosed to have liver metastasis. The remaining 35 patients received Imatinib post-operatively.

V. Conclusion

GISTs are rare sarcomas of the gastrointestinal tract. According to our study, the incidence of GIST is higher in males and in the age group of 51-60 years. The most common location of tumor is the stomach followed by the small bowel; in the small bowel the jejunum is typically involved. Patients with GIST generally present with symptoms of vague abdominal pain, mass per abdomen, and gastrointestinal bleeding; if the tumor has undergone obstruction or perforation, it will present acutely. CECT is the investigation of choice;features on CECT include extraluminal heterogeneous growth with a cystic and necrotic component; calcification is typically absent and no significant lymphadenopathy or metastasis are found. Additional imaging modalities to diagnose GIST include abdominal ultrasound, endoscopy, and at times abdominal radiograph. Histopathology and immunohistochemistry are more reliable for the diagnosis; IHC reveals that c-KIT mutations are frequently present. The tumor is classified into low, intermediate, and high risk based on tumor size and mitotic index.

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