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CLINICOPATHOLOGICAL CHARACTERISTICS OF GASTROINTESTINAL STROMAL TUMORS: A 10 YEAR EXPERIENCE AT TERTIARY CARE CENTRE IN INDIA

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ABSTRACT **Introduction:** Gastrointestinal stromal tumors (GISTs) are rare mesenchymal tumors of the gastrointestinal tract (GIT) and account for even less than 1% of all GIT tumors. Stomach is the most common site, but GISTs may arise from anywhere in the GIT. GISTs usually present with Pain abdomen, bleeding or sign and symptoms of mechanical obstruction. **Materials And Methods:** Retrospective analysis of the patients of GISTs, who presented to Department of Radiation Oncology, Pt. B. D. Sharma PGIMS, Rohtak from the year 2011 to 2020, was done to analyze the clinicopathological characteristics of GISTs. **Results:** Total 36-patients of GISTs were identified, which constituted approximately 0.1% of total cancer patients (32,354) seen from the year 2011 to 2020 in Department of Radiation Oncology, PGIMS, Rohtak. The median age of presentation was 59-years (range 28-66); sixth decade of life was the most common presentation. Male to female ratio was 1.1:1. Tobacco intake was seen in 63.9% patients, while 41.7% were alcoholic. Out of 36 patients, 72.2% belonged to rural area. The most common presentation was pain abdomen (63.9%), lump abdomen (22.2%), and rest were vomiting, hemoptysis and hematemesis. Most common site of presentation was stomach (63.9%), followed by jejunum (22.2%), sigmoid colon (11.1%) and duodenum (2.8%). Out of these, 86.1% patients were C-KIT (CD 117) positive, 27.8% each were SMA positive & 25% were Vimentin positive and two patients were Caldesmon positive. At the time of initial presentation, 66.7% patients were of high grade type. Most common histopathological type of presentation was spindle cell type in 69.4% patients. Out of all patients, 36.1% patients presented with tumor size more than 10.0 cm. Majority of the patients i.e. 80.6% were locally advanced (stage III & IV), while 41.7% patients presented with lymph node metastasis. The most common metastatic site was liver (36.1%) followed by pancreas, bone and pleural effusion. **Conclusion:** In this retrospective analysis, majority of the patients i.e. 80.6% presented in locally advanced stage. Sixth decade of life was the most common presentation. Clinically, pain abdomen and lump was common. The most common site was stomach. Approximately, 86% patients were CD 117 positive. The liver represented the most common site for metastasis. It is suggested from this study to develop proper geographical atlas of GISTs patients so that exact graphical plotting of the patients can be done in different parts of the country to establish the accuracy of the data.

KEYWORDS : GIST, CD 117, mesenchymal, stomach, mutation, tyrosine kinase

INTRODUCTION

Gastrointestinal stromal tumors (GISTs) are the rare and commonest malignant mesenchymal neoplasms of the GIT which account for less than 1% of all gastrointestinal malignancies [1]. GISTs arise from interstitial cells of Cajal (ICC) or their precursors which act as gastro-intestinal pacemaker cells and involved in GI motility [2,3]. GIST usually occurs after 40 years and is rarely reported in young adults and children [4]. GIST shows no gender disparity. GIST may arise all through the gastrointestinal tract (GIT) but most common sites are the stomach (60%), small intestine (35%), and less than 5% cases are seen in esophagus, omentum, rectum and mesentry [5].

The most common prognostic factors for GISTs are tumor size and mitotic index. GISTs of less than 2 cm have better prognosis as they are cured by surgical resection and GISTs of 10 cm or greater have poor prognosis. The number of mitotic cells per high power field (HPF) determines tumor behavior; less than 1 per HPF being benign, 1-5 considered potentially malignant and more than 5 considered malignant [6]. A better prognosis is seen in stomach GISTs [4,5]. Histologically, most common GIST is spindle cell type (70%), epitheliod type (20%) and rest mixed type [4].

The most common marker for GISTs is CD117, an epitope of KIT receptor tyrosine kinase. Around 95% of GISTs are positive for CD117. In 85 to 95% of GISTs, activating KIT mutations are found. The PDGFR alpha mutations are seen in approximately 8-10% of KIT negative GISTs [7]. These receptor tyrosine kinases activation play a key role in the pathogenesis of GISTs [8,9]. The high specificity and sensitivity of the KIT is very much helpful in differentiating GISTs from the other various mesenchymal tumors of GIT [10]. The KIT and PDGFR mutations in GISTs are mutually exclusive. PDGFR mutations are seen in stomach GISTs and epitheliod GISTs. These GISTs show less malignant course [11]. GISTs also express CD34 marker but it is not sensitive and specific. Smooth muscle actin protein (SMA) is expressed by 10-47% of GISTs [12]. SMA positive GISTs are located in small intestine whereas SMA negative GISTs are located in stomach usually [13].

Surgery is the cornerstone treatment in potentially resectable or localized GISTs [14]. In patients which are at potentially high risk for recurrence, tyrosine kinase inhibitor (TKI) like imatinib is indicated as adjuvant treatment [15]. In metastatic or unresectable disease, the treatment of choice is imatinib which is administered till disease progression [16,17]. In progressive disease, dose of imatinib is escalated only if no severe adverse drug reactions are present or may be switched to a second line TKI [18]. This study was aimed to review the patients of GISTs and determine their clinical and histopathological factors.

MATERIAL AND METHODS

In this retrospective analytical study, 36 patients were enrolled who presented in between 2011 to 2020 at our center. The GISTs were evaluated by contrast-enhanced computed tomography (CECT) scan and/or magnetic resonance imaging (MRI). The final diagnosis of GIST was made on the basis of histological / pathological examination and immunohistochemistry (IHC). The IHC profile included a panel of CD117, SMA, vimentin and Caldesmon. The platelet-derived growth factor receptor-alpha (PDGFRA) mutation analysis was not done in our institute due to limited resources. SPSS was used for statistical analysis. A p value of $<.05$ was considered statistically significant.

RESULTS

A total of 36 patients were enrolled in the present study. The clinicopathological characteristics of these patients are summarized in

Table 1. These 36 patients represented 0.1% of the all 32,354 patients who presented to Radiation Oncology Department, Pt BDS PGIMS, Rohtak; between 2011 to 2020. The median age was 59 years (range 28-66) with a male to female ratio of 1.1:1. Sixth decade of life was the most common (55.6%) presentation and 88.9% patients presented in 41 to 70 years age group. Out of 36 patients, 63.9% patients were smokers and 41.7% were alcoholic. Majority of the patients (72.2%) belonged to rural region and the rest belonged to urban. The most common presentation was pain abdomen (63.9%) followed by lump abdomen (22.2%), vomiting (11.1%), hemoptysis (5.6%), hematemesis (5.6%), constipation (5.6%) and malena (2.8%). The most common site of GIST was stomach (63.9%) followed by jejunum (22.2%), sigmoid colon (11.1%) and duodenum (2.8%). The tumor size of all the patients ranged between 4.2 cm to 18 cm. The most common size was in the range 5-10 cm (50%) then >10 cm (36.1%) and <5 cm (13.9%).

On histopathology, most common pattern was spindle cell pattern (69.4%) followed by epithelioid (16.7%), mixed (8.3%) and mesenchymal (5.6%). On IHC, C-KIT/ CD 117 expression was seen in 86.1% (31/36) patients. SMA expression was seen in 27.8% (10/36) patients, Vimentin expression in 25% (9/36) patients and Caldesmon expression in 5.6% (2/36) of patients. High grade GISTs were seen in 66.7% patients, intermediate grade in 8.3% and low grade in 25% patients. Nodes were found to be present in 41.7% of patients. Metastasis was seen in 15/36 (41.7%) patients at the time of presentation. Liver metastasis was seen in 13/36 patients, pancreas and bone metastasis was seen in 2 patients each. Ascites was seen in 19/36 patients and pleural effusion in 2 patients. At the time of presentation, stage IV was seen in 52.8% patients, stage III in 27.8%, stage II in 11.1% and stage I in 8.3% patients.

DISCUSSION

GISTs belong to the soft tissue sarcoma family but they are a complete different group due to their particular pathological characteristics and clinical behavior. There is significant variation in incidence globally from 0.4 to 2 cases per 1 lakh per year population [19]. Due to the rare presentation of GISTs, there are very few published literature on clinicopathological profile in Indian population. The incidence of GISTs was 0.1% of all cancer patients who presented to department during the stipulated time period, and this is similar to published literature [1,19]. Median age in this study was 59 years, which is in concordance with the published literature [4,19,20]. No case was reported in children in our study which is similar to published literature [19]. Male to female ratio (1.1) was also similar to the previous literature [5,7]. Our study observed stomach (64%) as the commonest site of disease which is consistent with Western literature [5,21] and Indian literature [22-24]. The most common histopathology in our study was spindle cell pattern which is similar to the literature [4,7]. The epithelioid type was seen in 16.7% which is less than the reported 20% incidence in the literature [7]. GISTs arising from the retroperitoneum and mesentry are extra-GISTs (EGIST) and constitute less than 10% of the patients; but no case of EGIST was seen in this study [25]. The clinical presentation of GISTs patients with abdominal pain, vomiting, abdominal lump, hemoptysis, hemetemesis and malena in this study is consistent with the published literature [26,27].

Cd117 expression / KIT mutation was seen in 86% of our patients which is slightly less than 95% previously published in the literature [7,19]. Surprisingly, 14% of our patients were found to be negative for CD117 / KIT mutation which is a rare thing to happen in GISTs [19]. The most common site for CD117 / KIT negative tumors was stomach (3/5 negative cases) and the other sites were sigmoid colon and jejunum having 1 case each. The DOG1 (Discovered On GIST 1) antigen is recently included in the IHC panel, which is highly specific and sensitive [28]. But, mutation testing for DOG1 was not done in this study due to limited resources. SMA expression was seen in 27.8% (10/36) of cases in this study which is similar to one study by Turner et al [12] but slightly higher than another study by Yakovenka et al (21.3%) [13]. All SMA positive GISTs were found to be positive for CD117/ KIT. SMA positive GISTs were found most commonly in stomach (60%) but it was lower than the CD117 positive cases (63.3%) [13].

In our study, at the time of initial presentation, 41.7% of GISTs were node positive. More than 50% of the patients with GISTs presented in stage IV, approximately 30% in stage III and rest 20% in early stage I & II GISTs. Out of 36 patients, 15 (41.7%) patients presented with metastasis. The most common site for metastasis was liver 13/15 patients (86%). Pancreatic and skeletal metastasis was observed in 2/15 (13.3%) patients. Pleural effusion was also present in 2/15 (13.3%) patients at presentation. On subgroup analysis, it was observed that 37.5% of patients in below 50 years age group presented with metastasis, whereas 42.9% of the patients in above 50 years age group. There was no significant relation between tumor size and grade and location. Among GISTs of less than 10 cm maximum dimension, 78.3% patients presented in stage III and IV; whereas among GISTs of more than 10 cm diameter, 84.6% patients presented in stage III and IV. Most of the GISTs were high grade (66.7%) followed by low grade (25%) and intermediate grade (8.3%) [19].

CONCLUSION

In nutshell, this study describes the single tertiary care centre experience of GISTs. In this retrospective study, most of the GISTs patients presented in locally advanced stage with abdominal pain and lump being the most common complaints. In majority, the patients presented in sixth decade of life with stomach as most common site. Approximately, 86% patients were CD 117 positive. The most common site for metastasis was liver. There were some similarities and some differences between this study and previously published literature. These differences could be attributed to the ethnic or genetic difference between Indian and global populations. However, one of the major limitations of this study is small sample size. It is recommended to conduct the study on larger population with longer follow up to have impactful data outcomes and better understanding of the GISTs.

Table 1. Clinico-pathological Characteristics And Results Of Mutational Analysis

Sr No.	Age (Y)	Sex	Subsite Involved	Histopathology	Immunohistochemistry		Grade	Size of Primary (cm)	Nodal status	Metastasis	Stage grouping
					C KIT / CD 117	Others					
1	60	F	Stomach	Spindle cell	Positive	-	H	7	N0	M0	IIIA
2	60	F	Stomach	Spindle cell	Positive	-	H	17	N1	M0	IV
3	65	M	Stomach	Spindle cell	Positive	Vimentin	H	14	N0	M0	IIIB
4	30	M	Stomach	Spindle cell	Negative	-	L	11	N0	M0	II
5	60	F	Jejunum	Spindle cell	Positive	-	H	13	N1	Pancreas, Bone	IV
6	50	F	Duodenum	Spindle cell	Positive	-	L	5.5	N0	M0	IB
7	60	F	Stomach	Spindle cell	Positive	SMA	H	5.5	N0	Liver	IV
8	55	M	Stomach	Epithelial	Positive	SMA, Vimentin	H	8.9	N0	Liver	IV
9	55	M	Jejunum	Spindle cell	Positive	-	H	8.3	N1	Liver	IV
10	55	M	Sigmoid colon	Spindle cell	Positive	SMA	H	18	N1	Liver	IV
11	28	M	Stomach	Spindle cell	Positive	Vimentin	L	17	N1	Liver	IV
12	60	F	Sigmoid colon	Mesenchymal	Negative	-	H	4.5	N0	M0	IIIA
13	50	M	Stomach	Spindle cell	Positive	Vimentin	H	6	N1	Liver	IV
14	66	M	Jejunum	Mixed	Positive	SMA, Caldesmon	L	4.5	N0	M0	I
15	42	F	Jejunum	Spindle cell	Negative	-	H	11.5	N1	Liver	IV
16	45	M	Stomach	Spindle cell	Positive	-	H	7	N0	M0	IIIA
17	58	F	Stomach	Spindle cell	Positive	Vimentin	I	9	N1	M0	IV
18	60	M	Stomach	Spindle cell	Positive	SMA	L	4.2	N0	M0	II
19	61	F	Stomach	Spindle cell	Positive	-	H	6	N0	M0	IIIA
20	60	F	Stomach	Spindle cell	Negative	-	H	7	N0	M0	IIIA
21	60	F	Stomach	Spindle cell	Positive	-	H	17	N1	M0	IV

22	65	M	Stomach	Spindle cell	Positive	Vimentin	H	14	N0	M0	IIIB
23	35	M	Stomach	Spindle cell	Negative	-	L	11	N0	M0	II
24	60	F	Jejunum	Spindle cell	Positive	-	H	13	N1	Pancreas, Bone	IV
25	60	F	Stomach	Epithelial	Positive	SMA	H	5.5	N0	Liver	IV
26	55	M	Stomach	Epithelial	Positive	SMA, Vimentin	H	8.9	N0	Liver	IV
27	55	M	Jejunum	Spindle cell	Positive	-	H	8.3	N1	Liver	IV
28	55	M	Sigmoid colon	Epithelial	Positive	SMA	I	18	N1	Liver	IV
29	28	M	Stomach	Mixed	Positive	Vimentin	L	17	N1	Liver	IV
30	60	F	Sigmoid colon	Mesenchymal	Positive	-	H	9	N0	M0	IIIA
31	66	M	Jejunum	Mixed	Positive	SMA, Caldesmon	L	4.5	N0	M0	I
32	42	F	Jejunum	Spindle cell	Positive	-	H	8.5	N1	Liver	IV
33	45	M	Stomach	Epithelial	Positive	-	H	7	N0	M0	IIIA
34	58	F	Stomach	Epithelial	Positive	Vimentin	I	9	N1	M0	IV
35	60	M	Stomach	Spindle cell	Positive	SMA	L	4.2	N0	M0	II
36	61	F	Stomach	Spindle cell	Positive	-	H	6	N0	M0	IIIA

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