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Evaluation of Gastro Intestinal Stromal Tumor in a Tertiary Care Center

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ABSTRACT

INTRODUCTION: Gastrointestinal stromal tumour (GIST) is an uncommon entity in clinical practice. It accounts for only <1% of all Gastrointestinal (GI) malignancies.
Stomach is the commonest site for this tumour. Other sites of GI tract are also affected with GIST.

AIMS AND OBJECTIVES: This study aimed evaluate the prognostic factors, and recurrence patterns among the patients of eastern India.

MATERIAL AND METHODS: This was a retrospective observational study which was conducted at the Department of Pathology in a tertiary care centre of eastern India. The specimens sent for HPE during the period June, 2018 to June, 2023 were included in the study. A total number of 2897 GI specimens sent to the Department for histopathological examinations were selected for the study. Out of which 77 specimens were diagnosed as GIST. The information of the vital parameters of the patient, type of tumour and type of treatments offered were collected for evaluation. The histological examinations relied on morphological features on Hematoxylin & Eosin stain and confirmation with immunohistochemistry markers CD34 and CD117 and S100. Patients with operable GIST underwent
Surgery followed by adjuvant therapy. Patients with inoperable/ borderline operable disease underwent neoadjuvant Tab. Imatinib 400 mg/day followed by reassessment for surgery.

RESULTS: The mean (±S.D.) age of the patients was 54.58±11.24 years with range of 28 -74 years and the median age was 54 years. 66.2% of the patients were with age< 60 years (p<0.001). Proportion of females (54.5%) was higher than males (45.5%) but it was not significant. Stomach (54.5%) was the most common site of tumour which was significantly higher than small intestine (27.3%) and large intestine (18.2%) (p<0.0001). At presentation non-metastatic cases (62.3%) were significantly higher than metastatic (35.1%) and locally recurrent cases (2.6%) (p<0.0001). In most of the cases the mitotic rate was between 5 – 10 /50 HPF (53.2%) which was significantly higher than mitotic rate <5/50 HPF (32.5%) and >10/50 (14.3%) (p=0.0042). Spindle cell type tumour (71.4%) was significantly higher than mixed (Spindle and Epithelioid) (20.8%) and Epithelioid type tumour (7.8%) (p<0.0001).

CONCLUSION: GIST is a rare tumor of the GI tract. It usually occurs in the stomach. The treatment of choice is surgery followed by adjuvant therapy.

KEYWORDS: Gastrointestinal stromal tumor, immunohistochemistry, micro GIST, surgery.

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INTRODUCTION

In 1983, Mazur and Clark first recognised “gastrointestinal stromal tumour” (GIST) as a unique variety of “stromal tumour”[(1)] . Some gastric tumours were diagnosed as leiomyomas or leiomyosarcomas . The tumors did not have all the features of smooth muscle or schwannian differentiation, but some features resembled myenteric nervous system. Perez-Atayde et al. noted ultrastructural

features of neuroectodermal differentiation and proposed that the cells of origin were the interstitial cells of Cajal.[2]. It has been seen that several factors influence the formation GIST like tyrosine kinase mutations, deletions of chromosomes 14q, 22q, 1p, and 15q . The mutation of tumour suppressor genes activate the formation from small, pre-clinical forms of GIST (micro GIST) to clinically detectable tumours with malignant potential [3]. Sarlomo-Rikala M. et al showed that CD 117 (KIT) is a specific IHC marker for GIST and some of them show immunohistochemical expression of CD34 and KIT in this tumor . This also supported the origin from the interstitial cell of Cajal lineage and differentiated GISTs from leiomyomas and gastric schwannomas [4]. The worldwide incidence and prevalence of GIST are estimated to be approximately 1.8– 2.2per 100,000 per year [5,6]. A Population based studies have shown that the median age at diagnosis is in the 60s, although GIST has been detected in all age groups. In some studies there is no significant sex difference. GIST in children and young adults is rare. There is a distinct subset of paediatric GIST, and syndromic GISTs may be found in children and individuals in early middle age[7]. Primary GISTs are commonly symptomatic (in about 80% cases), presenting with gastrointestinal bleeding or obstructive symptoms and abdominal pain. Incidental asymptomatic GISTs are discovered in less than 20% of cases during other gastrointestinal endoscopy or imaging investigations. The discovery of various diagnostic markers including mutational analysis for KIT protein CD 117 , PDGFRA and expression of protein kinase C and DOG1 help to distinguish GIST from other stromal tumours. The treatment of GIST has improved significantly over the last decade followed by remarkable improvements of the survival of patients[7].

We conducted a study among the patients who were diagnosed as GIST and treated at our hospital to evaluate the presenting symptoms, prognostic factors, and recurrence patterns among the patients.

MATERIALS AND METHODS

This was a retrospective and observational study conducted at the department of Pathology of a tertiary care hospital. All the specimens of Gastrointestinal system which were sent to the department of Pathology for histopathological examination report were reviewed. The laboratory investigations including complete blood counts, liver function tests, renal function tests, electrolytes, echocardiography, chest X-ray were also compiled. The specimens included surgical biopsy and excised specimens. The study was carried out over a period of 5 years, from June,2018 to June,2023. During this period, total 2900 GI specimens were sent to the Department for histopathological analysis. 8 cases were excluded from the study because non availability of paraffin blocks. 13 cases did not have the information about site of tumour were excluded. Total 2879 cases were taken and among them, 77 specimens were diagnosed as GIST. When the patient was first examined in the hospital , clinical history was taken. Patient data including age, sex, complaints,status at presentation , the extent of disease, history of prior treatment were noted. Complete data of clinical history were retrieved in case of retrospective cases . Then it was categorized as primary, metastatic or locally recurrent. The fresh gross specimens of the GI tract were examined and grossing was done for further processing. The gross specimen shown in (Figure A). After grossing and tissue processing Formalin fixed paraffin embedded (FFPE) tissue blocks were made. The tissue sections were taken on the slides and Hematoxylin and Eosin (H&E) stain was done. For 77 patients 781 blocks were examined. The diagnosis was established on the basis of histopathological examination . Microscopically different types of morphology were recognized (Fig. B,C,D) . After morphological diagnosis by H&E stain , immunohistochemistry CD117, CD34 and S100 were done for confirmation of the diagnosis. Immunohistochemistry markers CD34 and CD117 shown in (Fig. E,F)

The study variables were the patient, tumour and treatment. Tumour variables included site, mitotic rate, histomorphology, necrosis and size.

Patients with operable GIST underwent surgery followed by adjuvant therapy. Patients with inoperable/ borderline operable disease underwent neoadjuvant therapy. Tab. Imatinib 400 mg/day was given and then they were reassessd for surgery. Patients with metastatic disease received palliative Tab. Imatinib 400 mg/day . Patients not receiving any form of treatment or who had initial surgery elsewhere without proper report, were referred only for adjuvant imatinib, were not included in the analysis

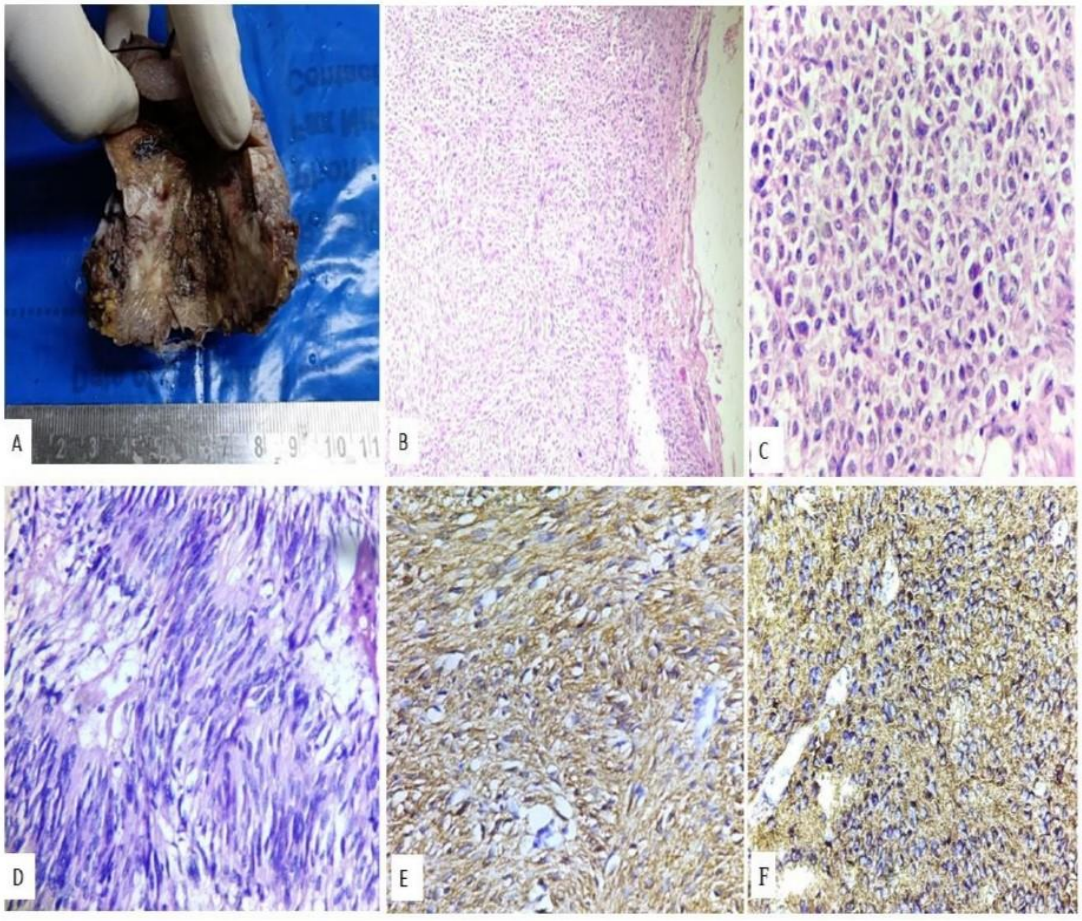

FIGURE A-GROSS IMAGE OF GASTRIC GIST SHOWING AREAS OF NECROSIS AND HAEMORRHAGE.

FIGURE B- H&E(100X) SHOWS TUMOR CELLS REPLACING THE NORMAL GASTRIC PARENCHYMA.

FIGURE C- H&E(400X) SHOWS GIST COMPRISING OF TUMOR CELLS HAVING EPITHELIOID MORPHOLOGY.

FIGURE D- H&E(400X) SHOWS GIST COMPRISING OF BLAND LOOKING SPINDLE CELLS ARRANGED IN SHORT FASCICLES.

FIGURE E- H&E(4OOX) SHOWS CD117 POSITIVE SPINDLE CELL TYPE GIST.

FIGURE F- H&E(400X) SHOWS CD34 POSITIVE GIST.

.RESULTS AND OBSERVATION

Total 77 GIST patients were studied in our hospital in the above mentioned time period.

Most of the patients were below 60 years at the time of presentation and diagnosis. The mean (±S.D.) age of the patients was 54.58±11.24 years, median age was 54 years and it was statistically significant.. Our age range was 17- 74. It occurs commonly below 60 years of age.The Female patients (54.5%) were more frequent than male (45.5%), but it was not statistically significant. The most common site was the stomach (42%) followed by the small bowel (21%). Other sites of tumour included the rectum, colon and retroperitoneum. It was statistically significant. Majority of the patients did not present with metastasis. 48 patients presented without metastatis. 2 patients had locally recurrent tumor. 27 patients came with metastasis. Some patients had liver metastasis from the GIST which is the commonest metastatic site. Some of them had undergone excision of an abdominal tumour two years ago. One patient aged 17 years presented with recurrent stomach GIST. She was undergone total gastrectomy with excision of mesenteric and right paracaval lymph nodes. Her whole body 18-FDG PET CT

report suggested metabolically active bilateral cervical, axillary, pelvic and Inguino-femoral lymph nodes due to metastatic involvement.

Table 1: Clinicopathological features of patients

Patients' characteristics				
Age (years)	Mean± S.D	54.58±11.24		
	Median	54		
	Range	17 – 74		
		Number	**%**	**p-value**
	>60 years	26	33.8	<0.0001 S
	<60 years	51	66.2	
Gender	Male	35	45.5	0.16 NS
	Female	42	54.5	
Site of tumour	Stomach	42	54.5	<0.0001 S
	Small intestine	21	27.3	
	Large intestine	14	18.2	
Status at presentation	Non-metastatic	48	62.3	<0.0001 S
	Metastatic	27	35.1	
	Locally recurrent	2	2.6	
Mitotic rate (HPF)	<5/ 50	25	32.5	0.0042 S
	5 - 10/ 50	41	53.2	
	>10/ 50	11	14.3	
Histopathological subtype	Spindle cell type	55	71.4	<0.0001 S
	Epithelioid cell type	6	7.8	
	Mixed (spindle + epithelioid)	16	20.8	

The mitotic rates of most of the patients (53.2%) was more than 5 – 10 / 50 HPF. In 14.3% it was more than 10 /50 HPF. This was also statistically significant. 71.4% of cases were reported microscopically as spindle cell GIST which was the most frequent morphological type. Only 6 cases (7.8%) showed epithelioid type GIST and 16 cases (20.8%) showed mixed spindle and epithelioid morphology. These findings are also statistically significant.

The postoperative histopathology and IHC markers were positive for CD34 and CD117 in all cases. CD117 was diffuse strong staining with perinuclear/cytoplasmic pattern in most cases; focal pattern of staining was noted in two cases.

DISCUSSION

GIST is the third most common tumor of the GI tract. In the past, these tumours were classified as leiomyomas, leiomyosarcomas and leiomyoblastomas, but it is now evident that GIST is a separate tumour entity[7]. The median age of our patients was 54.26 years which is comparable with other reported series from the Indian authors[8-10]. The oldest patient was 77 years old and the youngest was 17 year old.

All patients had initial laboratory investigations including complete blood counts, liver function tests, renal function tests, electrolytes, echocardiography, chest X-ray, ultrasonography (USG), and/or CECT of the whole abdomen. In most of the studies USG , CT scan and Contrast enhanced CT were the common investigation for the initial diagnosis of

these tumors[9]. In this series also we recommended the same investigations. MRI was rarely used.

GISTs were common in females in our series which is similar to some studies[9]. In some other studies GIST was seen more frequently in males[10,11]. The patients usually present with pain abdomen and gastrointestinal bleeding. G.Ravikumar et al found that 50 % of the cases of his series presented with gastrointestinal bleeding[10]. Almost all the patients had complaints of pain abdomen of insidious onset which later aggravated. Some patients also presented with melena. The most common site of tumour was stomach (54.54%) followed by small intestine (21%) in this series. This is also similar as other studies[8-10]. Lakshmi et al. reported equal rates of occurrence of gastric and small intestine GIST[11]. There are many factors which influence the recurrence. Many large studies have shown that the factors associated with high risk of recurrence include tumour size, location, mitotic index, type of KIT mutation, completeness of tumour resection, and intraoperative factors like tumour rupture and mucosal invasion[12]. Emory et al. reported the significance of prognostic factors to be site dependant[13]. According to some the most important factor for prognosis is the size and mitotic rate of the tumor[14-17]. Fletcher et al., under the National Institutes of Health, proposed risk stratification for GIST based on mitotic rate and tumour size[17]. Rutkowski. et al. added several other factors like site of the tumor, sex of the patient[18] . Similar findings have been observed in our study as well. We have also encountered that the the prognosis of stomach GIST is better than small intestine GIST. In our series also the patients having mitotic rate of > 10/50HPF were found to have poor survival. The average tumour size was around 9.5 cm. Size more than 10 cm was a predictor of poor survival.

In a study, Miettinen et al. described gastric GIST with two histological types -spindle cell type and epithelioid cell type. Most small intestine GISTs were spindle cell type with no further histological subtype. They believed that epithelioid subtype in small intestine GIST represents a morphologic manifestation of tumour progression[15]. Cho et al. in their studies of more than 1000 patients, found spindle cell tumours to have a better prognosis than epithelioid variant[19]. In our study,7.8% patients had epithelioid morphology which was associated with poor prognosis compared to the spindle cell type. Other factors which affect patient's survival significantly are- tumour spill, status of tumour presentation, KIT exon mutation and resected margin status[20]. According to some authors nuclear pleomorphism is an important factor for future recurrence[21]. We have also seen that the recurrent GISTs that we encounterd had nuclear pleomorphism.

The initial treatment of GIST was surgical resection with wide local excision. followed by Imatinib therapy. In inoperable advanced case the patients were treated with imitanib.This therapy improves the survival of the patients[22-24]. All our patients were treated with surgery with wide local excision. All our patients were treated with imitanib. The patients are doing well .

CONCLUSION

Gastrointestinal stromal tumors are rare malignant tumors of the GI tract. They can occur at any age but common in elderly. It occurs in both sexes. They present with pain or gastrointestinal hemorrhage. They may be diagnosed incidentally. The initial treatment by surgical resection followed by Imatinib therapy.

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