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Clinicopathological Study Of GIST In A Tertiary Care Centre: Two Years Experience

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Abstract

Background-. Gastrointestinal stromal tumors are the most common mesenchymal tumors of gastrointestinal tract (GIT). Present study was done to evaluate the clinicopathological features, treatment and its effects in these patients.

Methodology- This is a retrospective study conducted in two year period. 12 patients with confirmed histopathological diagnosis of GIST were taken and their epidemiological, personal, pathological and treatment data was collected from their hospital records.

Results– In the present study median age of patients of GIST was 51.1 years and were predominantly male (67%). The most common primary site was found to be stomach (67%). Out of 12 specimens, 10 were resection specimens of which one received Neo-adjuvant chemotherapy. Chronic abdominal pain and abdominal fullness were the most common presentation. Radiologically - solid, heterogeneous submucosal mass was present in all the patients. Mean size of tumor was 8.16 cm and had predominantly spindle cell morphology. Eleven patients had low grade and one had high grade disease. All patients presented with localised disease with no lymphovascular invasion and no metastasis. 9 patients were classified as low, one was very low and two were classified as high on risk assessment. IHC was available for 6 cases. Follow-up of all patients on treatment with Imatinib was available for 1 year in which no recurrence / metastasis was noted.

Conclusion- The present study provided clinicopathological characteristics and epidemiology of GIST in a tertiary care centre in 2 year period.

Keywords: GIST, Imatinib, IHC, Risk assessment, Sarcoma

Introduction

Gastrointestinal stromal tumors are the most common mesenchymal tumors of gastrointestinal tract (GIT).[1] They account for less than 1% of all gastrointestinal tumors and about 5% of all sarcomas.[2] Most commonly affected site is stomach followed by small intestine, colon and rectum and oesophagus.[3] Presentation of GIST is non-specific and varies from abdominal pain, gastric ulcer, gastrointestinal bleeding and can be an incidental finding in imaging studies.[4]

The initial assumption of smooth muscle origin of these tumors gave rise to assignations such as Leiomyoma or leiomyosarcoma, until ultrastructural and immunohistochemical studies negated this possibility.[5] Immunohistochemical markers for GIST are CD-117 and DOG-1.[3-6] Patients with GISTs without CD117 expression may harbour mutations in the platelet – derived growth factor receptor- α (PDGFR- α) gene or may have wild- type tumors with substantial reduction in the expression of succinate dehydrogenase.[6]

Complete surgical resection is the mainstay of treatment for GIST cases with localised disease.[6] Imatinib mesylate, a selective tyrosine kinase receptor inhibitor (TKI), is used as an adjuvant or neoadjuvant therapy to improve the morbidity and mortality associated with GISTs.[6] Due to growing resistance, sunitinib and regorafenib are effective second – line TKIs.[1]

Materials And Methods

Study Design

The present study was a retrospective study undertaken at a tertiary care centre, Jaipur, India, over a period of two years from January 2019 to December 2020. Information taken from all cases is epidemiological data, Personal data, pathological and treatment data. Follow up cases were taken for 1 year from January 2021 to December 2021.

Sample Size

12 histopathologically diagnosed GIST cases.

Study Participants

Inclusion criteria

Histopathological / IHC confirmed cases of GIST.

Exclusion Criteria

1. Non confirmed cases,
2. Resected specimens already proven on small biopsy for avoid doubling,
3. Already treated patients undergoing biopsy afterwords.

Sample Collection

Tissue samples from all suspected sites were received in 10% neutral buffered formalin for histopathological examination. The grossing was carried out on same day or next day as per fixation with special emphasis to anatomical orientation of specimen and done as per standard grossing guidelines. Tumor gross characteristics and site was noted. Representative sections taken are then processed, dehydrated and embedded with paraffin, 4 µm sections were serially cut on albumin coated slides and stained by Hematoxylin and Eosin (H&E). Sections were examined under light microscopy and detailed histopathological features were noted. Where ever required Immunohistochemistry done to confirm the diagnosis / For Tumor Categorization / Grading / Risk assessment. IHC was based on HRP polymerase system and consisted of CD117, DOG-1 and Ki67. Patient's demographic and clinical data, treatment data and follow up data was taken and analysed.

Results

A total of 12 patients of GIST were studied. Out of which 7 (67%) patients were male and 3 (33%) patients were female. Male: Female ratio was 7:5. Age predominance is between 40-50 years of age group which is 50% of all cases. The median age was 51.1 years. There was no history of smoking and tobacco chewing. The most common primary site was stomach (67%) followed by jejunum (17%), mesentery (8%) and transverse colon (8%). Clinically they presented predominantly with chronic abdominal pain and abdominal fullness (70%). On radiological examination, most tumors presented as solid, heterogeneous submucosal masses.

On Gross / Histopathological examination mean size of the tumor was 8.16 cm. morphologically spindle cell was the predominant type. On the basis of cytological features and mitotic activity tumor was graded as low (11 patients) versus high (1 patient). All patients presented with localised disease with no lymphovascular invasion and no metastasis.

Risk assessment was done on the basis of size, site and mitotic activity. Nine patients were classified as low, one was very low and two were classified as high on risk assessment. IHC was done on six cases in which one showed isolated DOG–1 positivity and rest showed both CD-117 and DOG-1 positivity. Ki67 Index is <5% in 4 cases, 6-8% in 1 case and >8% in 1 case. One year follow-up on treatment with Imatinib was uneventful with no recurrence / metastasis.

Discussion

Gastrointestinal stromal tumors are the most common mesenchymal tumors of gastrointestinal tract (GIT).[1] Most commonly affected site is the stomach followed by small intestine, colon and rectum and oesophagus.[3]

GIST affects mostly patients of adult age group. In the present study most cases were in age group of 40-50 years predominantly, and most common affected site was gastric. D. Brady – west et al in 2012 also found in their study, the mean age as 54.5 years.[5]

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Most common Clinical presentation in these patients were chronic abdominal pain and abdominal fullness. Hanam M. Alghamdi et al in 2019 found frequent symptom as abdominal pain in their study.[8] Others have found dyspepsia, diarrhoea, constipation and fatigue in these patients. Sometimes patients may land up in emergencies like perforation, bleeding and obstruction.

On radiology patients presented with solid, heterogenous submucosal mass. Sharma J et al in 2021 reported heterogeneously enhancing mass in their study as the most common presentation.[9] GIST can presented as intramural, mural or extra serosal which can be easily appreciated on CT scan. Mucosal ulceration can be seen in 50% of cases. The heterogenicity can be seen usually in large masses as seen in the present study.

Histopathologically most common morphology is spindle cell type. In the study by Zainab Al-Maqrashi et al in 2021, spindle cell morphology was the predominant type in the GIST.[6]

In the present study Mean size of the tumor was 8.16 cm. Jumniensk et al study in 2018 reported the mean size of tumor as 8.78 cm which is similar to the present study.[4] Size appears to be important prognostic indicator in these tumors, when tumor is of large size, necrosis, surface ulceration are commonly seen.

In the present study showed no lymphovascular invasion and metastasis were seen in the cases of GIST. However Trisha M. Parab et al showed lymphovascular invasion and metastasis in their study.[1]

Risk assessment was low in nine cases in present study. M. H. Eleanor koay et al in 2005 reported high risk assessment in 31cases in their study.[10] Risk stratification is very important in determining the treatment of these patients. In low risk cases, complete surgical resection without any therapy is indicated while in high risk patients / advanced disease, Targeted therapy with tyrosine kinase inhibitors are beneficial.

In present study < 5 per 5 mm² (low mitotic activity) mitotic rate were found in the cases of GISTs. Jumniensuk et al in 2018 found High mitotic counts per 5 mm2 were found correlated with metastasis.[4] mitotic activities are the most powerful prognosticators integrated with tumor size. Neo-adjuvant and adjuvant treatment is recommended for in patients with tumours > 4 cm and/or high mitotic count.

Antibodies used for IHC include those for KIT, desmin, S100 protein, α-smooth muscle actin (α-SMA), CD34, DOG1 (discovered on GIST-1), signal transducer and activator of transcription 6 (STAT6), β-catenin, and anaplastic lymphoma kinase (ALK). Ki-67 IHC is useful for risk evaluation of GIST recurrence.[14]

GIST should be differentiated from other mesenchymal tumors like Leiomyoma, Leiomyosarcoma, Schwannomas, neurofibroma, fibromas and fibromatosis. For identifying GIST, IHC was come up as a boom to diagnose and hence get accurate treatment of these patients. SMA, Desmin and Caldesmon may show positivity in both GIST and smooth muscle tumors however CD117 and DOG-1 will be negative in cases of smooth muscle tumors. Like ever nerve sheath markers like S-100 protein will be represented in both GIST and nerve sheath tumors but CD117 and DOG-1 will be seen only in GIST patients. Fibrous tumors will be show SMA, Bcl2, β- catenine positivity.

The role of Imatinib mesylate on patients with locally advanced and metastatic GISTs is good, leading to important gains in quality of life and survival.[3]

In most cases of GIST, activating c-kit mutation are found which is responsible for over expression of kit protein detected immunohistochemically. A minor proportion of cases show mutations in PDGFRA.

Imatinib is a tyrosine kinase inhibitor (TKI) that selectively inhibits KIT protein tyrosine kinase, BCR-ABL, and PDGFRA. It was approved in the adjuvant setting for resectable GIST, as well as in the palliative setting for unresectable/metastatic tumors, in the postoperative adjuvant setting and resectable GISTs, wide excision with margins negative surgery is curative for patients.[13] Minimal side effect of Imatinib therapy are nausea, vomiting, oedema and skin rash.[3]

Conclusion

GIST is the most common mesenchymal tumor of GIT. In view of their elaborative knowledge of pathogenesis and their treatment, these tumors can be

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treated very successfully. Hence proper diagnosis with accurate risk assessment is necessary to get proper treatment. Also rare presentation, morphology and immunohistochemical knowledge is required to accurately diagnose these cases. In the present study, it showed that most cases are of low grade and low risk; hence they can be treated adequately with a multidisciplinary approach.

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Fig1 : 200X H / E stained section of GIST showing spindle cells in fascicles

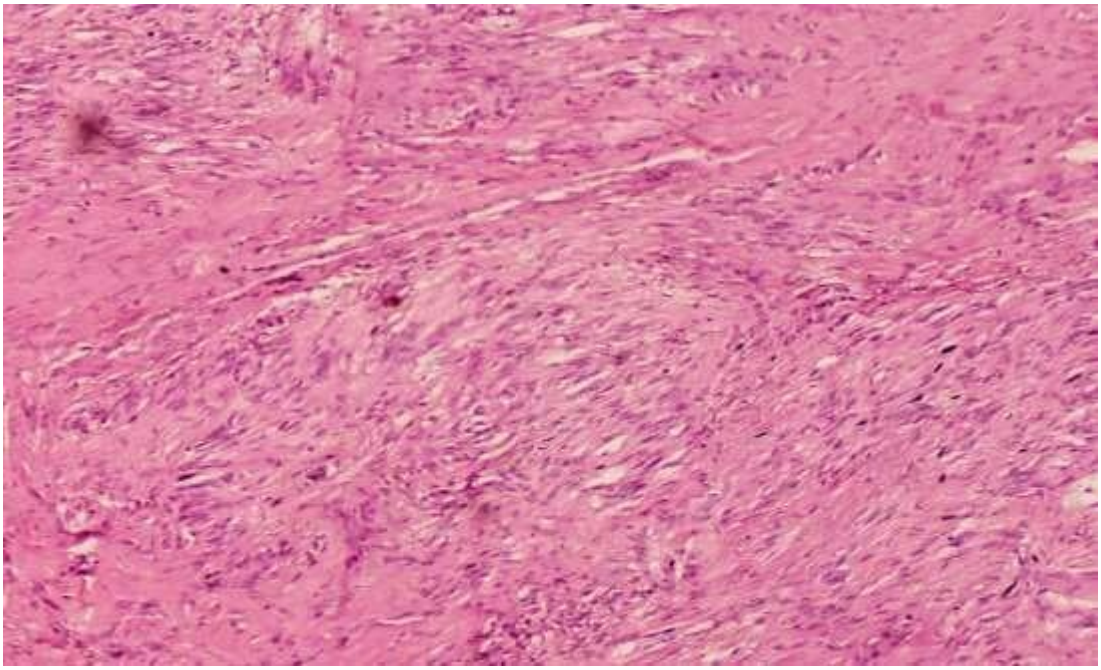

Fig 2 : DOG-1 cytoplasmic Positivity (400X) on IHC staining of tumor cells in GIST

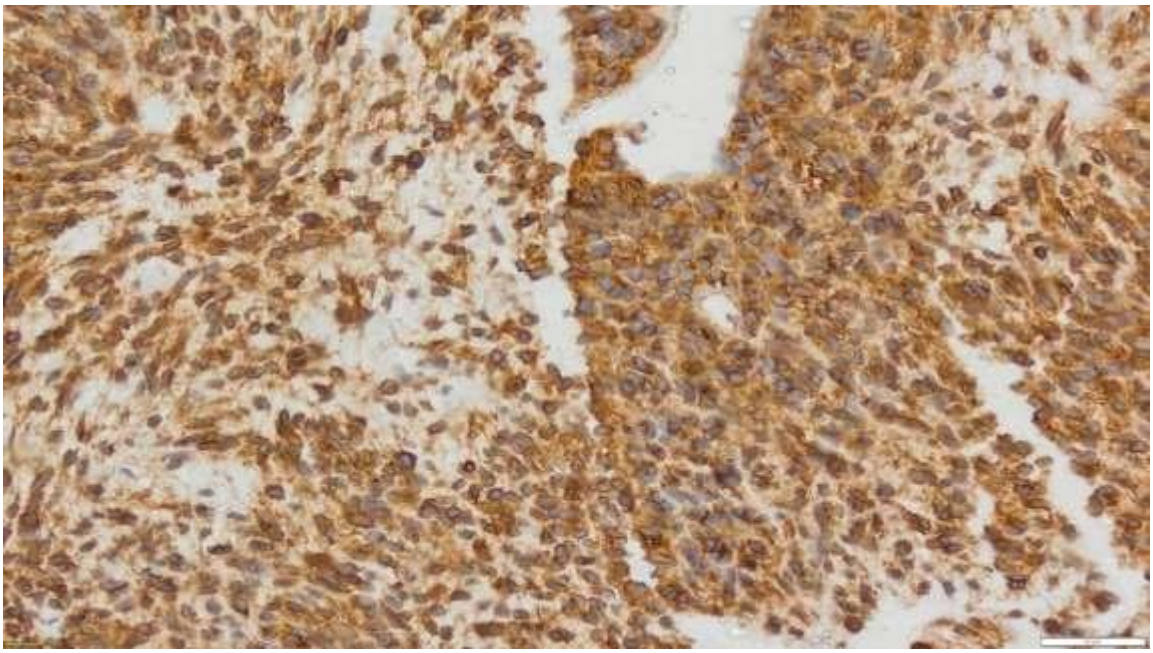

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Fig 3 : CD-117 cytoplasmic positivity (400X) on IHC staining of tumor cells in GIST

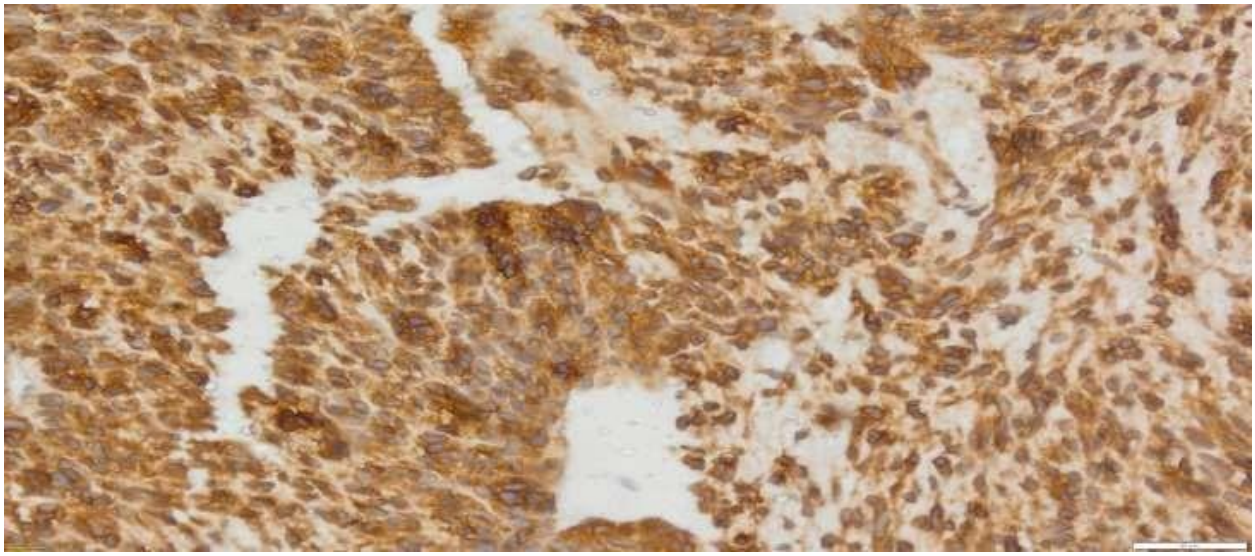

Fig 4 : Ki67 nuclear positivity (200x) on IHC staining of tumor cells in GIST

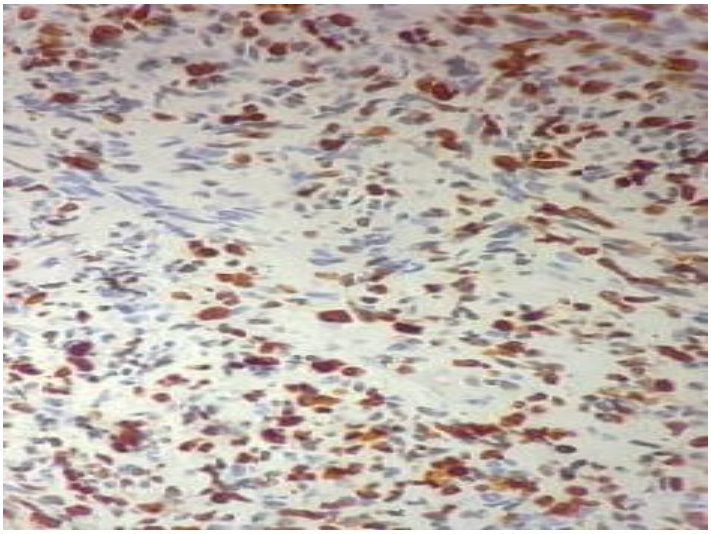

Table 1: Age wise incidence of cases of GIST

AGE (YEARS)	NO OF CASES	PERCENTAGE
40-50 years	6	50%
51-60 years	3	25%
61-70 years	1	08%
>70 years	2	17%
Total	12	100%

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Table 2: Distribution of GIST cases as per site

Location of Tumor	No of cases	Percentage
Stomach	08	67%
Jejunum	02	17%
Mesentery	01	08%
Colon	01	08%
Total	12	100%

Table 3: Distribution of cases of GIST on the basis of gender

Sex	No. Of cases	Percentage
Male	**7**	**67%**
Female	**5**	**33%**
Total	**12**	**100%**

Table 4 : Distribution of cases of GIST on the basis of Grading of tumor

Grade	No. Of cases	Percentage
Low grade	**11**	**92%**
High grade	**01**	**08%**
Total	**12**	**100%**

Table 5 : Distribution of cases of GIST on the basis of clinical features

Clinical Feature	No. Of cases	Percentage
Abdominal fullness with Pain	**10**	**83%**
Bleeding	**02**	**17%**
Total	**12**	**100%**

Table 6 : Distribution of cases on the basis of Risk assessment

Tumor parameters		Risk assessment			
Mitotic rate	**Size**	**Gastric**	**Jejunum**	**Mesentery**	**Colon**
< 5 per 5 mm2	**< 2 cm**	**2**	**0**	**0**	**0**
	>2 - <5 cm	**2**	**0**	**0**	**1**
	>5 - <10 cm	**3**	**1**	**0**	**0**

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	>10 cm	0	1	1	0
>5 per 5 mm2	<2 cm	0	0	0	0
	>2 - <5 cm	0	0	0	0
	>5 - <10 cm	1	0	0	0
	>10 cm	0	0	0	0

Table 7: Distribution of cases as per IHC markers

IHC markers	No. Of cases	Percentages
DOG-1	01	17%
CD117 + DOG-1	05	83%
Total	06	100%

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