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ORIGINAL RESEARCH

Histopathological Study of Gastrointestinal Stromal Tumors

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ABSTRACT

Background: Gatrointestinal stromal tumor (GIST), now the most common mesenchymal tumor of the gastrointestinal tract(GIT), has been frequently studied.

Objectives: Our aim was to study histopathology, demographic profile, histopathological grading, IHC property and behavior of Gastro intestinal stromal tumor(GIST)

Material & Methods: Retrospectively 50 cases were selected& studied from the department of histopathology of tertiary care hospital, Ahmedabad, India during june 2010 to june 2013

Results: 50 cases were studied in our study. Most common site was stomach(40%)followed by jejunum(18%), rectum(16%)& ileum(12%). Most common age group was 51-60 years. Most common presenting symptoms was abdominal pain (70%) Seventy percent of Gastrointestinal stromal tumor were positive for CD 117(KIT). Histologically majority of them had a pure spindle cell morphology. Eight patients (21%) had recurrent /residual mass of presentation.

Conclusion: In our study large number of Gastro intestinal stromal tumor were present in the stomach. Most common age group was 51-60 years. Majority of them were of pure spindle cell morphology. Molecular studies and larger numbers of cases are required for meaningful conclusion to be drawn.

Key Words: GIST, IMMUNOHISTOCHEMISTRY

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INTRODUCTION

GIST as a concept originally developed with the realization that tumours traditionally diagnosed as GI leiomyomas or leiomyosarcomas markedly deviated from features expected of smooth muscle tumours for example these tumours lacked the ultrastructural features or were immunohistochemically negative for desmin, unlike their soft tissue counterparts.[1]

GISTs has been a subject of intense basic and clinical research for last one decade and more so were in vogue after the recent understanding on their molecular pathogenesis, namely common presence of activating mutations in gene encoding KIT, which has clinical significance making it necessary to correctly define an diagnose these tumours an separate them from mesenchymal tumours of abdomen[2].

GISTs are specific mesenchymal tumours of the GI tract that may occur along the entire GI tract, from oesophagus to anus and sometimes even in omentum an mesentery adjacent to stomach/intestines but separate from them. These tumours have wide clinical spectrum from benign, small, incidentally detected nodules to frankly malignant tumours[3].Gastrointestinal stromal tumours range in size from tiny tumours discovered incidentally, during tests for other diseases, measuring less than 10 mm to very large lesions measuring upwards of 350 mm (median 50 mm)[4]. Gastrointestinal stromal tumours share many features that can be identified by electron microscope and immunophenotyping with the interstitial cells of Cajal[5.6.] The interstitial cells of Cajal are innervated cells associated with Auerbach's plexus that have autonomous pacemaker function and coordinate peristalsis throughout the gastrointestinal tract.

GISTs are most common mesenchymal tumours of GI tract an ironically the most confusing and neglected area of both surgical pathology and clinical oncology until 2001, when a consensus conference held at National Institute of Health provided a solid, evidence based rationale for diagnosis an prognostication of GIST's[4].

Definition: GISTs are define as cellular, spindle cell, epitheloid or occasionally pleomorphic mesenchymal tumours of GI tract that express KIT (C117) protein as detected by immunohistochemistry[7]. Few exceptions exist to this definition which include lesions having typical cytoarchitechtural features of GIST but which:

1. Appear to be IHC inert (e.g. Due to fixation artefact, excessive heat during section drying).
2. Are KIT negative use to sampling error (e.g. very small needle biopsies)
3. Have ceased to express KIT due to some form of clonal evaluation, perhaps following STI-571 therapy.
4. In very small percentage(<2%) of otherwise typical tumours that lack either KIT mutations or KIT over expression.

Table 1: Cytologic and Morphologic Patterns of GIST[(59)]

Cytologic types	Growth patterns
Spindle cell	Fascicular
Round (epitheloid cell)	Storiform
Plasmacytoid cell	Palisaded
Signet ring cell	Diffuse, sheet like
Granular cell	Organoid(nested)
Mutinuceated cell	Myxoid

Gastrointestinal stromal tumours are often discovered incidentally by CT or endoscopy. Endoscopic ultrasound is very accurate in locating lesions on the wall of the gastrointestinal tract[7,8]

MATERIALS AND METHODS

A retrospective study of patients with GIST enrolled at tertiary care hospital, Ahmedabad, Gujarat from June 2010 to June 2013 was carried out. As mentioned previously in definition of GIST, majority are neoplasms of GI tract, but these known to occur in mesentry,

retroperitoneum and pelvis are also included in the study. A case files with diagnosis of GIST were obtained and evaluated and analyzed with respect to histopathological parameters which included the gross appearance of tumour, size etc. Type of material on which histopathological examination (HPE) was done consisted of small biopsy, specimen or large biopsy or slides for review that was received at the institute was noted from patient's case files.

Light microscopic findings, which include pattern (spindle / epitheloid /other), differentiation (smooth muscle / neural / uncommitted), skenoid fibers (extracellular collagenous globules) and coagulative necrosis (with ghosts of tumour cells) were noted. The amount of mitoses was counted per 50 consecutive high power fields from the most cellular or mitotically active areas.

For the purpose of clinic-pathologic correlation, the GIST's were divided into six categories.

1. 2-5 cm with mitosis <5/50 hpf
2. >5-10 cm with mitosis <5/50 hpf.
3. >10cm with mitosis <5/50 hpf.
4. 2-5 cm with mitosis >5/50 hpf
5. >5-10 cm with mitosis >5/50 hpf.
6. >10 cm with mitosis>5/50 hpf.

Immunohistochemistry slides were retrived from the filing system. In cases of lost or broken slides, immunostains were applied on freshly cut sections. Immunohistochemistry panel evaluated consists of c-kit(CD 117),CD34,actin,S-100,desmin and vimentin.

RESULTS

In present study, most common age group is 51-60 of age and average age at presentation was 55 years, range being 21 years to 75 years.The study showed a male predominance. Out of total 50 patients,31(62%) were males and 19(38%) were females.In present study, the major chief presenting complaint was abdominal pain (in 35 patients). All the patients had visited the hospital with symptoms, none of them were discovered incidentally.

Table 2: Age Distribution

Study	Median Age
PN Cooper et al[9]	62 years
Miettinen[10]	56 years
B P Rubin[11]	58 years
Present study	55years

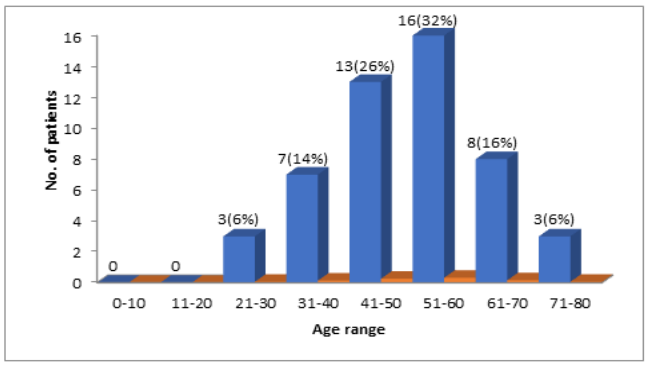

Figure 1: Age Distribution

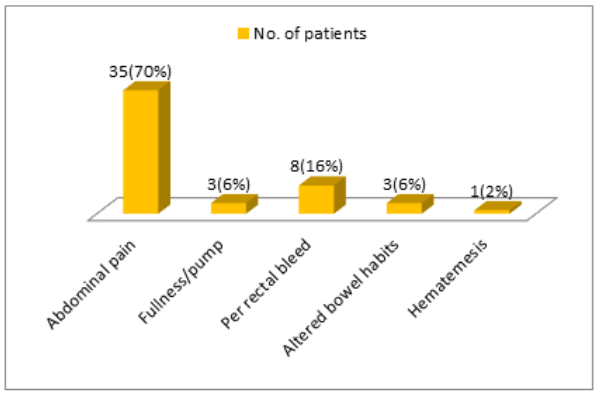

Figure 2: Presenting complaints

In present study, the most common primary site was stomach (40%) followed by jejunum(18%) rectum(16%), ileum (12%), colon (6%) , duodenum (2%) retroperitoneum (4%). In one of the patient presenting as liver metastasis, the primary could not be identified. Spindle cell morphology amounted to 76% of tumours, 6% showed pure epitheloid pattern, 18% showed mixed features.

Table 3: Primary site of tumor

Site	Cooper et al[9]	Miettinen[10]	B P Rubin[11]	Present Study
Stomach	68%	49%	56%	40%
Small intestine	24%	28%	22%	30%
Large Intestine	8%	18%	20%	22%
Other	0	5%	2%	8%

In 33(66%) of the 50 patients, the tumour showed <5 mitosis/50 hpf and the remaining 17 (34%)had mitosis >5/50 hpf.

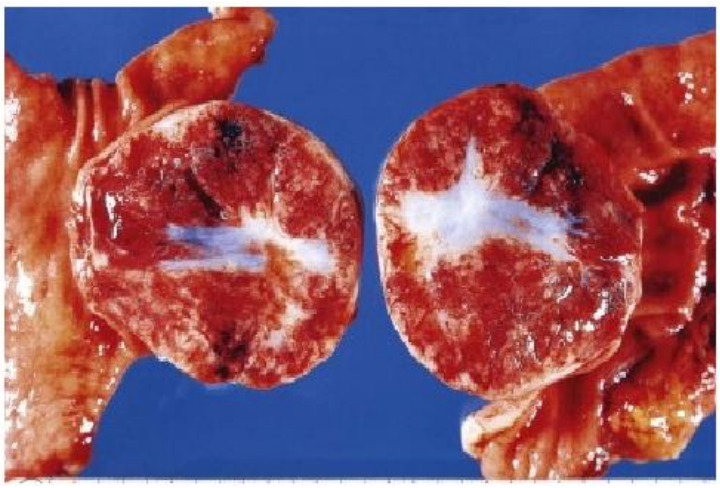

Figure 3
Gross appearance of GIST. A, This example is polypoid and has a large central scar.

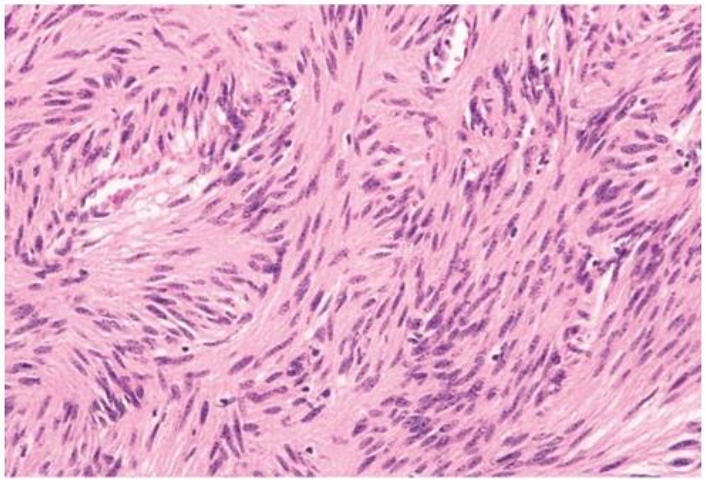

Figure 4
Typical low-grade spindle cell gastrointestinal stromal tumor (GIST) composed of interlacing fascicles of cells with cigar-shaped nuclei

Table 4: Relation of Mitosis according to size tumor

Size of tumor	No. of patients with <5/50 hpf mitosis	No. patient with >5/50 hpf mitosis
2-5 cm.	7	2
>5-10 cm	22	11
>10 cm	4	4
Total	33	17

Table 5: We Can Divide Gist Into 3 Categories as Below

Category	No. of patients	Percentage
Low grade	9	18%
Intermediate grade	22	44%
High grade	19	38%

From above table, it is evident that 18% tumours presented as low grade, 44% as intermediate grade and 38% as high grade.
C-kit was positive in 70% of cases, CD34 in 36%, action in 34%, while desmin and S-100 in 18 and 8% respectively. Vimentin was positive in 98% cases. 8 out of the 50 patients were metastatic at presentation. 12 patients were lost to follow up. 8 (21%) patients out of 38 patients had recurrent/residual mass of presentation.

DISCUSSION

A total of 50 patients were enrolled from June 2010 to June 2013 in the present study of the clinical profile of Gastrointestinal stromal tumours. A comparative analysis has been done with other similar studies performed in the past.
The median age at presentation in present study was 55% years. The range being 21 years to 75 years. In the study of P N cooper et al[9] (1991) median age of presentation was 62 years, review by Miettinen[10] (2001) showed the median age was 56 years, while that in study of B P Rubin[11](2006) it was 58 years. These two age distributions are comparable for age of presentation; GIST is the tumour of middle aged to elderly age group.

Out of the total 50 patients in our present study, 31(62%) were males and 19 (38%) were females. Cooper et al[9] enrolled a total of 100 patients in their study and in that 55% were males & 45% were female. While in Miettinen[10]study there is 61% males and 39% females. In the B P Rubin[11] study there is almost around equal sex distribution.So, from all above study, male dominance is found in GIST patients.

The most common primary site was stomach (40%), followed by small intestine 30% and large intestine 22% and other sites were 8%.In the study by cooper et al[9], the following were primary sites of disease: Stomach 68%, small intestine 24%, large intestine 8%.In the study by Miettinen[12], Stomach 49%, small intestine 28%, large intestine 18%, other 5%.In the study by B P Rubin[11], Stomach 56%, small intestine 22%, large intestine 20%, other 2%Thus, stomach remains the predominant site of the primary tumour in all the studies.

Abdominal pain was presenting symptoms in 70% of the cases, followed by bleeding per rectum in 16% cases, fullness or lump & altered bowel habits each 6% of cases and hemetemesis in 2% of cases.Cooper[9] found GI bleeding in 29 cases , followed by pain on 28 cases, palpable mass and weight loss in 6 cases each, anorexia and lethargy in 5 cases each, altered bowel habits and vomiting in 2 cases.

Spindle cell constituted 76%, epitheloid were 6% while 18% showed mixed pattern. Cooper et al too found spindle cell as the dominant morphology (65%) Rubin[11] mentions epitheloid morphology to be common in stomach however no such correlation could be established on this study. In the study by Miettinen[13] the tumors were relatively monotypic with spindle cell (86%), epitheloid (5%), or mixed patterns (9%).

It should be noted that morphology is not an independent factor suggesting degree of malignancy, it has to be supported by other Histological features. Such as cellularity, necrosis & haemorrhage.

66% consisted of tumours showing <5/50hpf mitosis while 34% showed >5/50hpf mitosis. So, according to table mentioned in results for risk of stratification 9(18%) cases were typified as low risk, 22(44%) cases as intermediate risk and 19(38%) cases as high risk. So ,majority of cases presented in intermediate risk category.

8 (16%) patients showed metastatsis disease as presentation, 6(75%) tumours showed metastatsis to liver while 2(25%) tumours metastasized to lymphnode.

70% of cases showed CD117 positivity, CD34 positivity was seen in 36% cases, while actin, desmin and S-100 showed 34%,18% and 8% cases positivity respectively. Vimentin positivity was seen in 98% tumours.

The comparative study by Rubin[9] states CD117 positivity in 95%, CD34 in 60-70%, actin, desmin and S-100 in 30-40%, 5% and 2% respectively. In the study by miettinen[14] there was CD117 expression was detected in 91% of the cases, CD34 in 82%, smooth muscle actin in 18%, and desmin in 5%;

The low results in present study for CD117 may be due to:

1) small size of biopsy for gist is known to be focally positive.
2) Immunoreactivity is sometimes lost in metastatic disease.
3) Post chemotherapy stastus.

Low CD34 positivity may be attributed to malignant GISTs which are many times CD34 negative.

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