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ORIGINAL ARTICLE

Clinicopathological profile of gastrointestinal stromal tumours in a tertiary care centre in Jammu region

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Abstract

Background: Gastrointestinal stromal tumour (GIST) is a soft?tissue sarcoma of the gastrointestinal (GI) tract. These are known to arise from the interstitial cells of Cajal. The aim of this study was to understand the clinical, histopathological, immunohistochemical characteristics of GISTs in a tertiary care centre. **Material Methods:** This study comprises of 45 patients who were diagnosed as GIST and were registered in the department of Pathology from 1st May 2018 to 31st August 2021. The demographic and clinicopathological data was collected and analysed carefully. **Results:** Most of the patients presenting with GIST were in the 6th decade (23 cases, 51.1%) with females (35 cases, 77.8%) being more commonly affected than males. Stomach was the most common site of origin (30 cases, 66.7%) in our study, with abdominal pain (18 cases,40%) being the most common presenting symptom. Spindle cell type was the most commonly reported histological type in 35 cases (77.8%). 80% of GISTs showed low mitotic counts. Majority of cases (35 cases, 77.8%) belonged to intermediate risk category.**Conclusion:** With the availability of various risk categorization systems, GISTs can be treated on the basis of assessment of array of prognostic factors, risk of metastasis and recurrence which will further aid in lowering the morbidity and mortality associated with GISTs.

Key Words

CD117, DOG-1, Gastrointestinal stromal tumour, GIST

Introduction

Gastrointestinal stromal tumor (GIST) is the most common soft?tissue sarcoma of the gastrointestinal (GI) tract affecting 16-20 people per million per year in Asian population while it affects 10-15 people per million per year in western countries. [1] GISTs can be categorised as gastrointestinal, with stomach and small intestine being the most common primary GI site or extra gastrointestinal GIST which arise outside of the gastrointestinal tract in omentum, mesentery or retroperitoneum. Before the understanding of molecular pathogenesis of GIST, most GISTs were earlier diagnosed as leiomyoblastomas and gastrointestinal autonomic nerve tumors (GANTs).[2] Gastrointestinal stromal tumours (GIST) are known to arise from the interstitial cells of Cajal, which are also known as 'pace makers' of the gastrointestinal tract. These tumours display a broad spectrum of clinical presentation from being asymptomatic to rapidly progressive malignancies. Although the etiology of GISTs is mostly sporadic, yet some of them are associated with syndromes like succinate dehydrogenase
complex deficiencies, neurofibromatosis type 1 (NF1), Carney Stratakis syndrome, Carney triad and PDGFRA-activating germline mutations. Most GISTs show immunoreactivity to CD 117, except for 5-10% of GISTs which are negative for CD117 and mostly contain PDGFRA mutations.[3]

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Material & Methods

Patients who were diagnosed with GISTs between 1st May 2018 and 31st August 2021 were identified by reviewing the archives at the Department of Pathology in the Government Medical College, Jammu after getting permission from the institutional ethics committee vide no. C-228. 45 cases were identified as GISTs along with their hematoxylin and eosin (H&E) slides and CD117 and DOG-1 immunostained slides were also available for reexamination. All the available clinical data such as age, gender, tumour location, tumour size, presenting signs and symptoms were properly analysed. The hematoxylin and eosin (H&E) slides from all cases were retrieved and reexamined keeping in mind the various parameters like histological type (whether spindled, epithelioid, or mixed), microscopic arrangement , cellularity, degree of nuclear atypia , cellular pleomorphism, cytoplasmic appearance, skeinoid fibers, type of stroma (myxoid, sclerotic), hyalinized blood vessels, peritumoral lymphoid infiltration, calcification, hemorrhage and necrosis. Immunohistochemical reactivity with antibodies against Cluster Differentiation (CD)117 and Discovered On Gist-1 (DOG1) was noted.

Inclusion Critria

1. All the patients with histologically confirmed GIST whose paraffin-embedded tissue blocks were available in the Department of Pathology, Government Medical College, Jammu.
2. GISTs that were diagnosed on morphology but were KIT- negative.

Exclusion Criteria

1. Patients with GISTs whose paraffin-embedded tissue blocks were unavailable in the Department of Pathology, Government Medical College, Jammu.
2. Patients presenting with mesenchymal tumours other than GISTs arising from the gastrointestinal tract, retroperitoneum and presenting as intra-abdominal masses.

Results

Demographic profile: The study group comprises of 45 patients of which, there were 10 males (22.2%) and 35 females (77.8%). The age of the patients ranged from 28 to 80 years, with mean age of 53.55 years and male: female ratio of 1:3.5. The maximum number of patients who were diagnosed with GIST were in the 6th decade (23 cases, 51.1%) followed by the 5th decade.

Clinical profile: The most common presentation was abdominal pain in 16 cases (35.6%), followed by asymptomatic in 13 cases (28.8%), gastrointestinal bleeding in 6 cases (13.4%), anemic symptoms and gastrointestinal obstruction in 5 patients each (11.1%). GIST was found to be most commonly found to be located in stomach in 30 cases (66.7%), followed by the small intestine, colon and rectum. The size of the tumour ranged from 1.5 cm to 20.0 cm. In majority of cases, size of GIST was in range of > 5-? 10 cm (23 cases, 51.1%).

Pathological profile:Most of GISTs were unifocal (40 cases, 88.9 %) while multifocality was seen in 5 cases (11.1%). In our study, spindle cell type was reported as the most common histological type, accounting for 35 cases (77.8%), followed by mixed spindle and epithelioid type in 5 cases (11.1%) and epithelioid type in 3 cases (11.1%).

The spindle cell type of GIST were further subcategorised as diffuse hypercellularity (27cases, 77.1%), palisade vacuolated (6 cases, 17.1%), and sclerosing (2 cases, 5.8%). All the cases of epithelioid GISTs were of diffuse hypercellularity subtype. The mixed spindle-epithelioid histology cases were subcategorised as diffuse hypercellularity subtype (2 cases, 66.7%) and palisade-vacuolated subtype (1 case, 33.3%).

The microscopic arrangement of the tumour cells revealed interlacing bundles in 35 cases (77.8%) and solid pattern in 10 cases (22.2%). High cellularity was reported in 40 cases (88.8%), whereas 5 cases (11.2%) showed moderate to low cellularity. Low-grade nuclear atypia and mild nuclear pleomorphism was reported in 37 cases (82.2%). The cytoplasm of the tumour cells varied from mixed clear and eosinophilic cytoplasm in 60% cases to pure eosinophilic cytoplasm in 40% cases. Skeinoid fibers were seen in 7 cases (15.5%). Intratumoral lymphocytic infiltrations were found in 8 cases (17.7%). Sclerotic stroma was present in 6 cases (13.3%). Myxoid change was reported in 4 cases (8.8%). Tumour necrosis was reported in 17 cases (37.7%).

Low mitotic counts (? 5/5mm2) were reported in 36 cases (80%) and high mitotic counts (> 5/5mm2) were reported in 9 cases (20%).

Immunohistochemistry studies revealed that 39 cases (86.6%) were immunoreactive for CD 117 and showed diffuse and strong cytoplasmic staining while 6 cases did not show immunoreactivity for CD 117 but showed strong and diffuse positivity for DOG-1 in tumour cells.

Discussion

The mesenchymal tumours are rare tumours of the gastrointestinal system. Amongst these, GISTs are the most common tumours followed by other tumours like leiomyoma and leiomyosarcoma. These tumours are actually known to originate from interstitial cells of Cajal. The majority of patients presenting with GIST were in 6^{th} decade (23 cases, 51.1%), followed by 5^{th} decade which was comparable to other studies carried out by

Table 1. Clinical Profile

Variables	Number of patients (%)
Age	
<30 years	2 (4.4%)
30-60 years	34 (75.6%)
>60 years	9 (20%)
Gender	
Male	10 (22.2%)
Female	35 (77.8%)
Clinical presentation	
Abdominal pain	16 (35.6%)
Asymptomatic	13 (28.8%)
Gastrointestinal bleeding	6 (13.4%)
Anemia	5 (11.1%)
Gastrointestinal obstruction	5 (11.1%)

Table 2. Pathological Profile

Variables	Number of patients (%)
Tumour location	
Stomach	30 (66.7%)
Duodenum	3 (6.7%)
Jejunum	6 (13.2%)
Colon	3 (6.7%)
Rectum	3 (6.7%)
Tumor size	
=2 cm	2 (4.5%)
>2- =5 cm	10 (22.2%)
>5-=10 cm	23 (51.1%)
>10- =15	8 (17.7%)
>15-=20 cm	2 (4.5%)
Histological features	
Spindle cell type	35 (77.8%)
a. Diffuse hypercellularity	27 (77.1%)
b. Palisade vacuolated	6 (17.1%)
c. Sclerosing	2 (5.8%)
Epithelioid type	5 (11.1%)
Diffuse hypercellularity	5 (100%)
Mixed spindle-epithelioid	5 (11.1%)
a. Diffuse hypercellularity	3 (60%)
b. Palisade vacuolated	2 (40%)
Low mitotic counts	38 (84.4%)
High mitotic counts	7 (15.6%)

Soreidea *et al.* [4] Females were far more commonly affected than males with a male: female ratio of 1:3.5 in our study. This was comparable to a study carried out by Dutta *et al* [5] whereas in studies conducted by Lakshmaiah *et al* [6] and Aggarwal *et al* [7] , males were predominantly affected with a male :female ratio of 2:1 and 1.7:1 respectively. The patients may present with a wide array of symptoms or may not show any symptoms at all. In this study, abdominal pain was the most common clinical presentation, followed by asymptomatic presentation (*Table I*) which was comparable to studies conducted by Aggarwal *et al* and Varsha *et al*.[8] The most common site of origin of GIST in our study was the stomach followed by small intestine, colon and rectum, which is similar to studies conducted by Parab *et al* [9] & Varsha P *et al*. GISTs arising from sites other than stomach are known to have a high malignant potential as compared to those arising from stomach. About 10% to 30% cases of GISTs may show malignant transformation.[10] Most GISTs present as exophytic growth which was noted in 70% of our cases while intraluminal or mixed growth occur less frequently. These tumours are known to express CD117 antigen (C-Kit), a gain of function mutation, which is held responsible for activating the growth of these tumours. Few cases of GISTs are associated with PDGFRA mutation or with neither CD117 nor PDGFRA mutation, which are called as wild type GISTs.[11] In our study majority of cases (39 cases, 86.6%) were immunoreactive for CD117 while 6 cases which were negative for CD117, were immunoreactive for DOG-1. This finding was comparable with a study conducted by Kisluk *et al*.[12] DOG-1 is a more sensitive and specific marker than CD 117, especially in a subset of KIT-negative GISTs.[13] GISTs can be diagnosed by various imaging modalities like abdominal ultrasound, CT scan, magnetic resonance imaging (MRI), and positron emission tomography (PET). Abdominal ultrasound, although is not a primary modality but is useful in GISTs larger than 5 cm and depends on other factors like presence of necrosis, ulceration, air in bowel and operator expertise .[14]

CT enterography is a very useful diagnostic modality used to know the actual location of these tumours, presence of any perforation, invasion of these tumours into nearby structures, or metastasis. GISTs are classified on the basis of size, as small (<5 cm), intermediate (5-10 cm), or large (>10 cm) based on visualization with CT imaging.[15] The size of majority of GISTs in our study ranged from >5-? 10 cm in 51.1% cases (*Table 2*) which was comparable to studies conducted by Jumniensuk *et al*.[16] On CT, small GISTs are seen as symmetric masses, which are well demarcated with sharp borders and usually exhibit intraluminal growth patterns. Intermediate-sized GISTs are comparatively less symmetrical, may exhibit both intraluminal and extraluminal growth patterns, and usually show evidence of infiltration to other organs. Large GISTs exhibit aggressive behaviour and are associated with peritoneal or distant metastasis.[17] MRI is a preferred

Fig I. Gross specimen showing a gastrointestinal stromal tumour arising from the wall of the small intestine (thick arrow showing GIST and thin arrow pointing towards the intestinal mucosa).

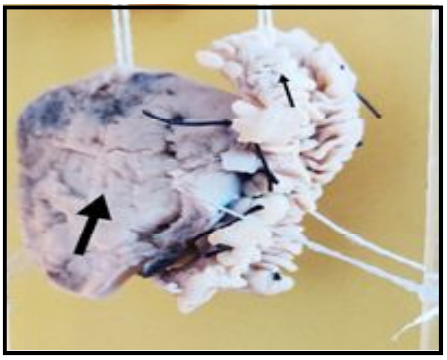
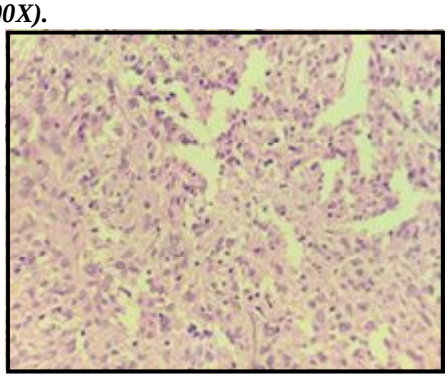


Fig 3. Photomicrograph showing GIST- Epithelioid cell type (H&E, 400X).



modality in case of rectal GISTs, liver metastasis, haemorrhage, and necrosis of tumours. Positron emission tomography scan (PET) or CT scan are useful in identifying necrotic areas in lesions and also help in distinguishing benign tumours from the malignant ones .[18]

The diagnosis of GISTs can also be made on endoscopic biopsies in asymptomatic cases especially and on surgically resected specimens in symptomatic cases. Microscopically, GISTs can be spindle shaped, epithelioid or mixed spindle and epithelioid types.[19] In our study, spindle cell type emerged as the most common histological type of GIST accounting for 35 cases (77.8%) which was similar to various study conducted by Jumniensuk *et al* [16]

Various classification systems have evolved over the years to classify GISTs for risk stratification purpose. The first classification system was the NIH classification system. It evaluated the recurrence risk by categorizing patients into very low, low, intermediate, and high-risk groups by taking the size and mitotic activity of the tumour as the parameters. They concluded that, tumours of size

Fig 2. Photomicrograph showing GIST - Spindle cell type (H&E, 400X).

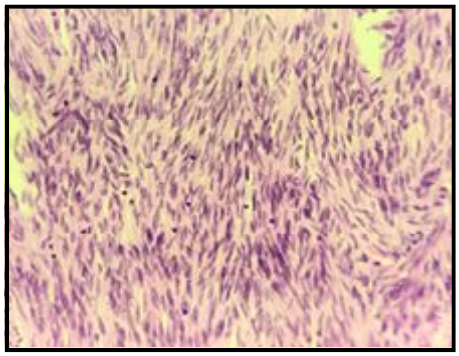
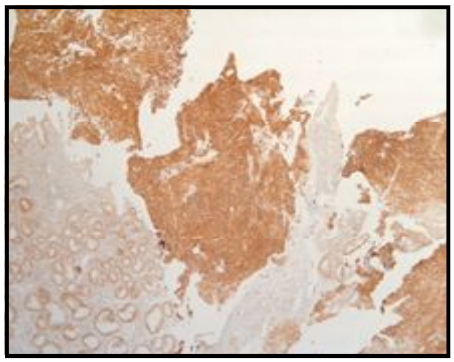


Fig 4. Photomicrograph showing strong and diffuse positivity for DOG-1 in spindled tumour cells. (DOG-1 Immunostain, 40X)



>5 cm in diameter along with a mitotic count greater than 5/50 high power fields (HPF) and tumours of size >10 cm with any mitotic count will have a higher risk of recurrence, subsequently requiring adjuvant drug therapy.[20]

Another classification system called the Armed Forces Institute of Pathology (AFIP) classification system has come into practice which concluded that anatomical location is an important prognostic factor in addition to tumour size and mitotic counts. This system was the first one to define the total area for mitotic counting (5 mm2). This classification system showed that the risk of recurrence for a tumour of the same size and mitotic count is greater for GISTs in non-gastric location rather than for GISTs arising in stomach.[21]

The French Federation of Cancer Centers Sarcoma Group (FNCLCC) and the National Cancer Institute (NCI) system are the most widely accepted grading scales for grading soft tissue tumours. The FNCLCC grading takes into account three parameters that is, mitotic count, necrosis, and differentiation of the tumour. According to this system, these factors have a strongly associated with presence of metastasis and high mortality rate.[22] The NCI system concluded that the assessment

of cellularity, cellular pleomorphism, and location of tumour determines the prognosis.[23] Majority of cases (35 cases, 77.8%) in our study belonged to intermediate risk category according to NCI system of grading, which is different from findings from study carried out by Jumniensuk C *et al*.[16] This categorization of GIST helps in assessing the risk of metastasis, recurrence and prognostication. These grading and staging systems of GISTs can be beneficial in determining the effectiveness of adjuvant therapy.

Conclusion

GISTs although are a rare subset of tumours, yet are the most common mesenchymal tumours of gastrointestinal tract. The majority of patients presenting with GIST were in the 5th and 6th decade. Abdominal pain was the most common clinical presentation stomach. The majority of the tumours presented with pure spindle cell morphology and 86.6% of the tumors were CD-117 positive, rest were DOG-1 positive.With the discovery of these mutations associated with these GISTs, the treatment has changed dramatically. Imatinib mesylate, a selective tyrosine kinase receptor inhibitor (TKI), is now being used as an adjuvant or neoadjuvant therapy to improve the morbidity and mortality associated with GISTs.

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Conflicts of Interest

There are no conflicts of interest.

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