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Original Research Article

Gastrointestinal stromal tumours: a clinico-pathological study

Nuvvula Satwik, Joseph Francis*, Natasha Mathias

Department of General Surgery, Yenepoya Medical College, Deralakatte, Mangalore, Karnataka, India

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***Correspondence:**
Dr. Joseph Francis,
E-mail: josephdiamondjoe@gmail.com

ABSTRACT

Background: The aim was to evaluate the clinical presentation, histopathological findings and immunohistochemistry in gastrointestinal stromal tumour (GIST) to better understand the disease.
Methods: Patients admitted and suspected to have GISTs in the Departments of General Surgery and Oncology, Yenepoya Medical College from the period of October 2016 to October 2018 were included in the study.
Results: From October 2016 to October 2018, 10 patients had been diagnosed with gastro-intestinal stromal tumour in Yenepoya Medical College. Out of the 10 patients 7 were males and 3 females. The age distribution showed that more than 70% of the cases were above the age of 55 years. Stomach was the most common site of GIST. The most common histopathological type was spindle cell type of GIST, and 70% of the GISTs came positive for CD117.
Conclusions: To conclude, Gastro intestinal stromal tumours are a rare entity. In this study conducted in a tertiary centre only ten cases were reported in a span of two years of the study period. Further analysis of age and gender distribution, histopathological and immunohistochemistry of these tumours suggested that in majority, age group was found to be above 55 years, with male preponderance. Commonest site was stomach (40%) followed by jejunum. Common histopathological finding was found to be spindle cell variant. 70% cases were CD117 positive with more than 5 mitotic figures/50 high power fields.

Keywords: Gastrointestinal autonomic nerve tumours, Gastrointestinal stromal tumours, Immunohistochemistry, Interstitial cells of Cajal, Platelet-derived growth factor receptor alpha, Positron emission tomography (PET) scanning using fluorodeoxyglucose

INTRODUCTION

Gastrointestinal stromal tumours (GISTs) are rare neoplasms. Although they represent only 0.1-3% of all gastrointestinal (GI) malignancies, they account for 80% of gastrointestinal mesenchymal neoplasms. In the last 12 years, the understanding and treatment of GIST has witnessed remarkable advances due to two key developments: (1) the identification of constitutively active signals [oncogenic mutation of the *c-kit* and platelet-derived growth factor receptor alpha (PDGFRA) gene-encoding receptor tyrosine kinases] and (2) the development of therapeutic agents that suppress tumour growth by specifically targeting and inhibiting this signal (imatinib mesylate, sunitinib malate).

These developments in the management of GIST represent a proof of the principle of translational therapeutics in oncology, confirming that specific inhibition of tumour-associated receptor tyrosine kinase activity may be an effective cancer treatment.[1-5]

Receptor tyrosine kinase receptors

In a landmark publication in 1998, Hirota and colleagues reported two critical findings: (1) near-universal expression of the transmembrane receptor tyrosine kinase KIT in GIST, and (2) presence of gain-of-function mutations in the corresponding c-kit proto-oncogene.[6] The KIT receptor is activated by binding its cytokine ligand known as steel factor or stem cell factor.[7] KIT

plays a critical role in the development and maintenance of components of hematopoiesis, gametogenesis, and intestinal pacemaker cells. GISTs are now identified by immunohistochemical staining for the CD117 antigen, part of the KIT receptor, in the appropriate histopathologic context. CD117 expression is characteristic of most GISTs but not of other gastrointestinal smooth muscle tumours such as leiomyosarcoma, which are more likely to express high levels of desmin and smooth muscle actin.[8-10] Application of CD117 staining as a diagnostic criterion for GIST has altered understanding of the prevalence of this disease.

Over 85% of GISTs have activating *KIT* mutations.[8] These mutations commonly occur in exon 11 (in 57-71% of cases), exon 9 (10-18%), exon 13 (1-4%), and exon 17 (1-4%).[11,12] Some GISTs may stain strongly for KIT (CD117) by immunohistochemistry (KIT-positive) yet lack KIT mutations, while others that do not stain for KIT (KIT-negative) may nevertheless harbour KIT mutations.[8] Approximately 35% of neoplasms lacking KIT mutations have activating mutations in a gene encoding a related receptor tyrosine kinase, the PDGFRA. PDGFRA mutations have been identified in exon 12 (1-2% of GISTs), exon 18 (2-6%), and exon 14 (<1%).[13] Finally, a few GISTs, the so-called wild-type (WT) GISTs, exhibit no detectable KIT or PDGFRA mutations and presumably have alternative pathways for pathogenesis. Recently, additional putative mutations have been identified. A BRAF exon 15 mutation was identified in a small percentage of WT tumours.[14] Insulin like growth factor 1 receptor (IGF-1R) over expression was documented in some WT GISTs as well.

Cellular origin of GISTS

The interstitial cells of Cajal (ICCs), sometimes referred to as the gastrointestinal pacemaker cells, form the interface between the autonomic innervation of the bowel wall and the smooth muscle itself.[17] They have the immunophenotypic and ultrastructural features of both smooth muscle and neuronal differentiation and serve to regulate peristalsis. Because GISTs, similar to ICCs, express KIT protein and two-thirds of GISTs also express CD34, a link between the two has been proposed.[15] It is assumed that GISTs originate from CD34-positive ICC stem cells within the wall of the gut and differentiate toward the pacemaker cell phenotype.[18-20]

In support of the origin of GISTs from ICCs, resected tumours have been accompanied by diffuse ICC hyperplasia in the adjacent gut wall (Auerbach plexus) in several kindreds with familial GIST.[19-22]

Nevertheless, the curious fact of primary GISTs arising outside of the gastrointestinal tract in the omentum and mesentery, or even in the retroperitoneum [often referred to as extragastrointestinal stromal tumours (EGIST)], remains. These are phenotypically identical to true GIST lesions of gastrointestinal tract origin.[23,24] While this finding seemingly contradicts the hypothesis of GISTs arising from ICCs within the gut wall, it is thought that these tumours arise from ICCs that were accidentally dispersed during embryogenesis.[19,21]

Histopathology

GISTs arising in the gastrointestinal tract are typically found in a subepithelial location. As they grow, bigger tumours can cause epithelial ulceration.

The cellular morphology of GISTs ranges from predominantly spindle shaped to epithelioid in character. Histologically, the appearance of these tumours usually falls into one of three relatively uniform categories: Spindle cell type- 70 percent, Epithelioid type- 20 percent, Mixed type- 10 percent.

GISTs of the spindle cell type are composed of relatively uniform eosinophilic cells arranged in short fascicles or whorls.[17] The nuclei tend to be uniform, and there may be juxtanuclear cytoplasmic vacuoles and nuclear palisading. Stromal collagen is minimal in most cases, and stromal hemorrhage is a common feature. Marked cytologic pleomorphism is rare and should raise the possibility of an alternative diagnosis if present.

Epithelioid GISTs are composed of rounded cells with variably eosinophilic or clear cytoplasm.[25] They tend to have round to oval nuclei with vesicular chromatin, and the architecture may be nested, potentially leading to confusion with an epithelial or melanocytic neoplasm. Interestingly, epithelioid type GISTs are more often KIT-expression negative, harbour platelet-derived growth factor receptor alpha *(*PDGFRA*)* mutations, and present most often in the stomach.[26-36]

GISTs of the mixed type may have areas of abrupt transition between spindle and epithelioid areas or complex intermingling of both cell types throughout.

The most prominent diagnostic marker of GIST is over expression of the receptor tyrosine kinase KIT (CD117), which is easily identified by positive immunohistochemical staining. Some instead harbour activating mutations in the PDGFRA gene. Importantly, however, DOG-1 (discovered on GIST-1) and PKC-theta (protein kinase C theta) are two immunohistochemical markers that are positive in GIST irrespective of *KIT*/*PDGFRA* mutational status.[31]

Immunohistochemical staining can help to distinguish GIST from other subepithelial tumours that may arise in the gastrointestinal tract.

Clinical manifestations

GISTs occur throughout the gastrointestinal tract from the esophagus to the anus. Within the gastrointestinal tract, GISTs are most common in the stomach (40 to 60

percent) and jejunum/ileum (25 to 30 percent). The duodenum (5 percent), colorectum (5 to 15 percent), and esophagus (≤1 percent) are less common sites. Tumours lacking any association with the bowel wall have been referred to as extragastrointestinal stromal tumours (EGISTs) and occur in the retroperitoneum, mesentery, and omentum.[26] The presentation varies depending on the primary tumour location.

Some GISTs are asymptomatic and are discovered incidentally during an endoscopic study or on cross-sectional imaging done for another purpose. More often, they are associated with nonspecific symptoms (i.e., early satiety, bloating), unless they ulcerate, bleed, or grow large enough to cause pain or obstruction.[19,20]

In general, the distribution of clinical presentation is as follows: overt or occult gastrointestinal bleeding- 28 percent (small intestine) and 50 percent (gastric), incidental finding (asymptomatic)- 13 to 18 percent, abdominal pain/discomfort- 8 to 17 percent, acute abdomen- 2 to 14 percent, asymptomatic abdominal mass- 5 percent.

Paraneoplastic syndromes are rare in GIST; however, potential paraneoplastic syndromes have been reported in a few patients, including consumptive hypothyroidism and non-islet cell tumour hypoglycemia.[27] GISTs frequently metastasize to the liver and peritoneum, and rarely to regional lymph nodes. They uncommonly metastasize to the lungs, the most common site of metastasis for softest tissue sarcomas.

Differential diagnosis

The differential diagnosis of a subepithelial tumour arising in the gastrointestinal tract is broad and can include GIST, leiomyosarcoma, leiomyoma, malignant melanoma, schwannoma, malignant peripheral nerve sheath tumour, fibromatosis (desmoid tumour), inflammatory myofibroblastic tumour, or even metaplastic ("sarcomatoid") carcinoma.

The distinction is usually based upon immune-histochemical and molecular analytic techniques, although there is some overlap:[30]

A key distinguishing point is the near-universal expression of KIT by GISTs. Approximately 95 percent of GISTs are KIT positive.

Another useful immunohistochemical stain is DOG-1 (discovered on GIST-1), which is expressed in nearly all GISTs, including KIT-negative platelet-derived growth factor receptor alpha (*PDGFRA*)-mutant tumours.[31-34]

Moreover, 60 to 70 percent of GISTs are positive for CD34, 30 to 40 percent for smooth muscle actin, 5 percent for S-100 protein, and 1 to 2 percent for desmin or keratin.[16,29]

Diagnosis and work up

The diagnosis of GISTs is based on morphology, positive immunohistochemistry (IHC) results for CD117 and DOG1, and mutation analyses of KIT and platelet-derived growth factor receptor α polypeptide gene (PDGFRA).[4] With increasing use of abdominal computed tomography (CT), magnetic resonance imaging (MRI) and endoscopy, an increasing number of asymptomatic GISTs are diagnosed at an early stage, although the effect of early detection of GIST on the prognosis remains unclear. Positron emission tomography (PET) scanning using fluorodeoxyglucose (FDG-PET) is highly sensitive for detecting tumours with a high glucose metabolism, including GIST; however, it is not sufficiently specific to make a preoperative diagnosis. The National Institute of Health (NIH) and Armed Forces Institute of Pathology (AFIP) risk classification criteria are commonly used to predict the prognosis of GISTs.[6] Large tumour size, high mitotic rate, non-gastric tumour location and tumour ulceration are commonly accepted to be associated with a poor prognosis in patients with GIST. Other factors including sex, age, symptoms and IHC results are also reported to be associated with patient outcomes.[7,8]

METHODS

After ethical committee approval and informed consent, patients diagnosed with GISTs were taken into the study. Examination and routine investigations were done. Management of the disease was recorded.

Study design

It was a time bound study (observational study) which includes patients admitted and suspected to have GISTs in the Departments of General Surgery and Oncology, Yenepoya Medical College during the period of October 2016 to October 2018.

After following up with Medical Records Department of Yenepoya Medical College patients admitted with GIST in previous year and on discussion with statistician sample size has been calculated and taken as a time bound study.

Inclusion criteria

This included patients of all age group and cases clinically consistent with the diagnosis of GISTs.

Exclusion criteria

Excluded patients diagnosed to have abdominal tumours other than GISTs and patients already diagnosed to have GISTs and undergoing treatment.

Data collection was done, followed by data analysis using appropriate statistical methods.

Statistical analysis was done using SPSS software version 22. Descriptive statistics were computed for required outcome variables.

RESULTS

From October 2016 to October 2018, 10 patients had been diagnosed with gastro-intestinal stromal tumour in Yenepoya Medical College.

Table 1: Age distribution in the cases and their frequency.

Age (in years)	Frequency	Percent
35-44	1	10.0
45-54	2	20.0
55-64	4	40.0
65-74	2	20.0
>75	1	10.0
Total	10	100.0

In this study it was found that 70 % of subjects were above the age of 55 years (Table 1). 70% subjects were men (7) and 30% women (3), signifying a male preponderance (Table 2).

Table 2: Gender distribution among cases.

Sex distribution	Frequency	Percent
Female	3	30.0
Male	7	70.0
Total	10	100.0

Table 3: Shows the finding of GIST at different parts.

Part of the GIT	Frequency	Percent
Jejunum	2	20.0
1st part of duodenum	1	10.0
3rd part of duodenum	1	10.0
Stomach	4	40.0
Extra intestinal GIST	2	20.0
Total	10	100.0

Stomach with an incidence of 40% was the commonest site, followed by extra intestinal sites. Jejunum, 1st part of duodenum and 3rd part of duodenum followed closely with an incidence of 20%, 10% and 10 % respectively (Table 3).

Table 4: IHC marker CD117 being positive in most case.

IHC	Frequency	Percent
CD117+	7	70.0
CD117-	3	30.0
Total	10	100.0

KIT gene mutation was studied by immunohistochemical analysis of CD117 expression- which as per studies was found to be positive in majority of cases. In this study, 70% were CD117 positive cases. However, 30% which were microscopically diagnosed as GIST were found to be negative for CD117 (Table 4).

Table 5: Mitotic figures more than 5 mitotic figures/50 high power fields having a prognostic indication for GIST.

Mitotic figures	Frequency	Percent
>5 per 50	2	20.0
1-2 per 50	1	10.0
2 per 50	2	20.0
3per 50	1	10.0
4 per 50	1	10.0
5 per 50	1	10.0
<5 per 50	1	10.0
<1 per 50	1	10.0
Total	10	100.0

Analysis of presence of mitotic figures showed more than 5/50 high power fields studied, in 20% of cases. Only 2-3% of tumours <10 cm and <5 mitoses/50 HPFs metastasized, whereas 86% of tumours >10 cm and >5 mitoses/50 HPFs metastasized (Table 5).

In this study, spindle cell variant was found to be the common histological variant with an incidence of 50%, epithelioid 20% and mixed variant was 30% (Table 6).

Table 6: Histological variant of GIST.

Type of cell	Frequency	Percent
Mixed	3	30.0
Spindle cell	5	50.0
Epithelioid	2	20.0
Total	10	100.0

DISCUSSION

The aim of this study was to establish GIST as a rare entity amongst common presentations of Gastro Intestinal tumours. Most often it is a diagnosis of surprise, given the varied presentations and the number of cases identified. In this study conducted in Yenepoya Medical College over a span of 48 months, only ten cases of GIST were identified.

In this study it was found that 70% of subjects were above the age of 55, which was well in accordance with the evidence found in literature. Tran et al described in a study conducted between 1992 and 2000, the age-adjusted yearly incidence rate was 0.68/100,000 amongst 1458 study subjects with GIST.[37] The mean age at diagnosis was 63 years. In another study conducted by Mietinnin et al, GIST was concluded to be a disease of the elderly.[36]

In our study, 70% subjects were men and 30% women, signifying a male preponderance. However, there is no evidence to conclude this. Ma et al did a surveillance of patients diagnosed with GIST from 2001 to 2011 to formulate a male to female sex ratio of 1.37.[38] There are no studies on this significance, to conclude fairly that gender has a role to determine the diagnosis of GIST.

Stomach with an incidence of 40% was the commonest site, followed by extra intestinal sites. Jejunum, 1st part of Duodenum and 3rd part of duodenum followed closely with an incidence of 20%, 10% and 10 % respectively. The incidence of extra intestinal sites of GIST was higher in this study than reported in other studies. In literature, multiple studies have established stomach as the commonest site of occurrence of this entity, confirming the results of this study.[16] GISTs found in other parts of gastro-intestinal tract were reported as 30% in jejunum and ileum, 5% in duodenum, 4% in colorectum, and rarely in the oesophagus and appendix. GISTs can also occur in extra intestinal areas like the mesentery, retroperitoneum and liver, as noted in this study as well.

Post excision a detailed microscopic study was conducted to categorize the pathological type of GIST based on cell type, IHC markers and presence of mitotic figures. In this study, spindle cell variant was found to be the common histological variant with an incidence of 50%, epithelioid 20% and mixed variant was 30%. Mietinnin et al went further and classified spindle cell GIST into sclerosing, palisaded-vacuolated, hypercellular, and sarcomatous and epithelioid tumours into sclerosing, dyscohesive, hypercellular, and sarcomatous.[36] Such further sub classifications have a great role in genetic analysis and continuing research on treatment modalities at a genetic level for tumours like GIST.

KIT gene mutation was studied by imunohistochemical analysis of CD117 expression- which as per studies was found to be positive in majority of cases. In this study, 70% were CD117 positive cases. However, 30% which were microscopically diagnosed as GIST were found to be negative for CD117. This incidence was higher compared to that found in literature, which was only about 4-5% requiring mutational analysis to further confirm the results. In a study by Mietinnin et al, approximately 70% of GISTs were positive for CD34, 20-30% were positive for smooth muscle actin (SMA), 10% were positive for S100 protein and <5% were positive for desmin.[36] These markers were not compared in this study, and could be considered a limitation. However, it was irrevocably concluded that CD117 has a strong association with GIST, as is suggested in the general literature.[39]

Analysis of presence of mitotic figures showed more than 5/50 high power fields studied, in 20% of cases. This signifies higher grade of differentiation, which as per literature is a tool for prognostication of patient survival. As per studies, disease outcome was strongly dependent on tumour size and mitotic activity. Only 2-3% of tumours<10 cm and<5 mitoses/50 HPFs metastasized, whereas 86% of tumours>10 cm and>5 mitoses/50 HPFs metastasized.

With a small sample size of 10 from a hospital, the conclusions and interpretation have its own limitations and need to be confirmed by larger community based studies.

CONCLUSION

To conclude, gastro intestinal stromal tumours are a rare entity. In this study conducted in a tertiary centre only ten cases were reported in a span of two years of the study period. Further analysis of age and gender distribution, histopathological and immunohistochemistry of these tumours suggested that in majority, age group was found to be above 55 years, with male preponderance. Commonest site was stomach (40%) followed by jejunum. Common histopathological finding was found to be spindle cell variant. 70% cases were CD117 positive with more than 5 mitotic figures/50 high power fields.

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