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GASTRO INTESTINAL STROMAL TUMORS – A REVIEW OF LITERATURE

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ABSTRACT

Gastro intestinal stromal tumours (GIST) are the most common mesenchymal tumour of the gastrointestinal tract. These tumours can arise in any part of the gastrointestinal tract but are more commonly seen in stomach. It is recognised with recent studies that these tumours arise from interstitial cells of Cajal. These tumours show expression for CD117 and CD34 on immunohistochemical staining. The prognosis of the patients with these tumours correlates well with tumour size, its location and mitotic activity. The genetic markers like telomerase activity and KIT mutation are also the important prognostic factors. Tumours with KIT mutation show better response to tyrosine kinase inhibitor like imatinib. The histochemical markers are useful in diagnosing GIST with malignant potential accurately. This article reviews the epidemiology, pathogenesis, morphological features, clinical presentation and differential diagnosis of GIST.

KEYWORDS: These tumours show expression for CD117 and CD34 on immunohistochemical staining.

INTRODUCTION

The primary tumours of the gastrointestinal tract can be classified as epithelial and mesenchymal tumours. GIST account for less than 1% of all gastrointestinal tumours and nearly 5% of all sarcomas.[1] GISTs are generally more common in the stomach (60 %) and are less frequent in the colon (10%).

In this review, we intend to collate the updated information and evolving data about GIST so as to differentiate them from other gastrointestinal tract malignancies, which is critical in determining the appropriate treatment strategies.

Historical Overview

Initially GISTs were thought to be derived from smooth muscle cells or the nerve cells. In 1940, Golden and Stout categorized these tumors based on the morphology as leiomyomas, leiomyosarcomas and leiomyoblastomas.[2]

In 1960, it was reported that GISTs were completely different from smooth muscle tumour.[3] Later in 1983, the term 'stromal tumour' was officially used by Mazur and Clark.[4] In 1998 Hirota and colleagues demonstrated that most GISTs have gain-of-function mutations in the receptor tyrosine kinase KIT.[5] In 2003, Heinrich and colleagues discovered that some of the GISTs have mutations that activate a closely related receptor tyrosine kinase, platelet-derived growth factor receptor α (PDGFRA). They also observed that GISTs were almost identical with interstitial cells of Cajal (ICC), the pacemaker cells of the intestinal tract.[6] In late 2000, tyrosine kinase inhibitors were developed that block several targets, including KIT.[7]

Incidence of GIST

Globally, incidence of GIST is difficult to determine. However, the current estimation of incidence in European countries ranges between 11% to 14%.[8,9,10,11,12,13] A greater number of gastrointestinal stromal tumours occur in adults between age 40 and 80 years old, with an average age of 60 years.[14] A small number of GIST are seen in individuals younger than 40 years of age. Of the uncommon GISTs in children, some are related to the Carney triad, a nonhereditary syndrome of unknown etiology seen primarily in young females that includes gastric GIST, paraganglioma, and pulmonary chondroma. There is also an increased incidence of GIST in individuals with neurofibromatosis type 1. There is no gender preference seen in GIST.[1]

Biological origin of GIST

It is recognized that the origin of GIST is the interstitial cells of Cajal, (ICC) the pacemaker cells of the gastrointestinal muscularis propria. ICC are named after Santiago Ramón y Cajal, a spanish pathologist and nobel laureate who first discovered these cells in 1889. These cells are situated in the stroma of the villi, in auerbach's plexus, deep muscular plexus, circular muscular layer of the intestine, and around the acini and blood vessels of the pancreas. It was demonstrated that GISTs have

identical characteristics with ICC in terms of ultrastructural and immunophenotype.[15]

Oncogenic KIT and PDGRFA mutations and signalling pathways in GIST

GISTs arise when the mutation occurs in KIT gene and PDGFRA gene. Around 80% of GISTs have mutated KIT and 5% mutated PDGFRA.[16] KIT gene encodes a KIT receptor for a growth factor ligand called as stem cell factor (SCF).[17] The binding of SCF with KIT is vital in the development of ICC, reproductive cell, melanocytes, red blood cells and mast cells.[18]

These both receptors consist of an extracellular ligand-binding domain, a transmembrane domain, a juxtamembrane domain and a kinase domain.[19] The kinase domain consists of tyrosine kinase 1 (TK I) and tyrosine kinase 2 (TK II).[19] TK I is responsible for ATP-binding pocket and TK II is responsible for kinase activation loop.

In normal condition, the activation of TK II takes place when the signaling molecule binds to the receptor of the extracellular domain. This activates the cascade of several cell signaling pathways such as PI3K/AKT, JAK/STAT and RAS/RAF (Figure 1).[16,19] The pathway regulates cell division, translation, transcription and apoptosis of the cells.[19]

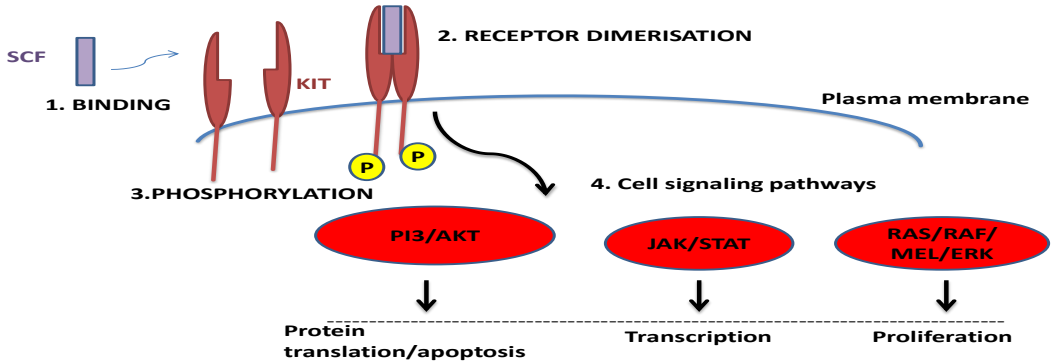


Figure 1: Schematic structure of KIT and PDGRFA receptor tyrosine kinases and distribution of KIT mutations in GIST.

Uncontrolled RTK activity results in the subsequent activation of the PI3K-AKT and MEK-MAPK pathways accompanied by a relatively low-level signal transducer and activation of transcription STAT1 and STAT3 activation. This leads to alterations in the cell cycle, protein translation, metabolism and apoptosis.[20]

Clinical Features

GISTs are commonly seen in the upper portion of the stomach (60%), jejunum and ileum (30%), duodenum (5%), colorectum (4%) and uncommon in the oesophagus and appendix (<1%),[21,22] Rarely, these tumours also seen to arise from an extra-gastrointestinal tract site such as omentum, mesentery and retroperitoneum.[14]

The spectrum of clinical presentation is wide and mainly related to tumour size. Commonly, the majority of GISTs remain quiet until the tumours are palpable. Small tumours are incidentally found during surgery, endoscopy or on imaging.[19] The large tumours usually present with GI bleeding. In the late stage, these tumours become palpable where they have already spread to the liver. These patients may present with lower-extremity oedema, ascites and jaundice.[1]

Pathological Features

Grossly, these tumors are well-circumscribed and highly vascular. The size of the tumour ranges from 1 to 35 cm with a median size of 5 cm.[3] The cut surface of the tumour appear fleshy pink or tan-white (Figure 2).[19] Larger tumours may undergo massive haemorrhagic necrosis and cyst formation.

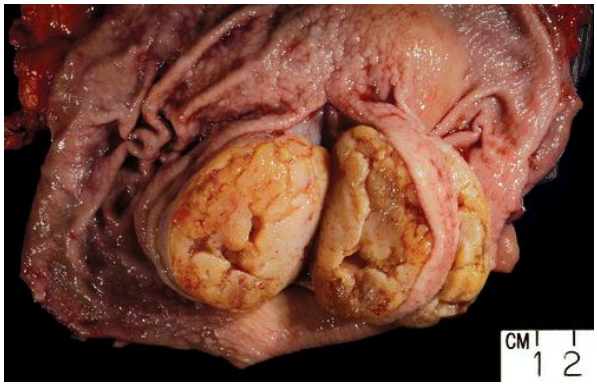
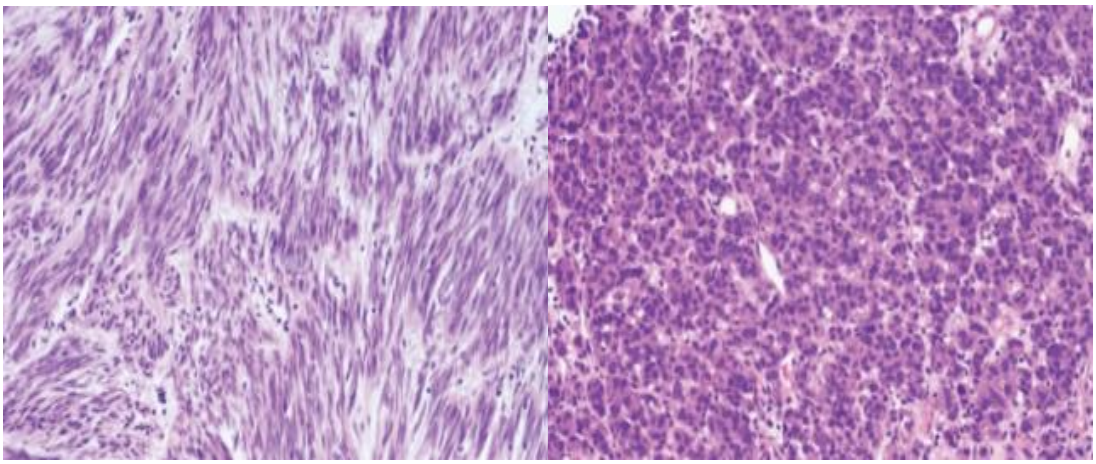


Figure 2: Macroscopic appearance of gastric GISTs.

Microscopic Features

GISTs presents in a variety of histological patterns such as spindle cells (70%), epithelioid cells (20%) and rest

are mixed cells.[3] Spindle cells are arranged in interlacing bundles and have elongated nuclei. It has pale-pink eosinophilic fibrillary cytoplasm, and ill-defined cell borders (Figure 3a).[3] Epithelioid cells are characteristically round cells with eosinophilic to clear cytoplasm and has vesicular nuclei (Figure 3b).[3]



3a **3b**

Figure 3a: Spindle cell GIST with (20X, Hematoxylin and eosin stain)
Figure 3b: Epitheliod cell GIST with (20X, Hematoxylin and eosin stain)

GIST Subtypes

Familial GISTs: Rarely GISTs present as heritable tumours where individuals inherit mutant KIT or mutant PDGRFA. These Patients develop multiple GISTs at younger age and may also have diffuse hyperplasia of Cajal cells.[19] These tumors are generally benign in nature.

Paediatric GISTs: Paediatric GISTs represent around 1% - 2% of all GISTs,[19] They are frequently misdiagnosed as some other acute or chronic abdominal condition. These tumours exhibit epitheloid morphology.[1] 10%-15% of paediatric GIST have either KIT or PDGRFA mutation.

Extragastrointestinal GISTs (eGIST): eGISTs are neoplasms that arise outside gastrointestinal tract and have clinicopathological and molecular profiles of GISTs.[23] These tumours are mostly located in the omentum or mesentery and rarely in retro peritoneum. Miettinen and colleagues observed that omental GISTs act in a benign way whereas more than half of the mesenteric tumours show malignant behaviour.[24]

Immunohistochemical markers for GIST: CD117 (c-Kit) is highly sensitive and specific marker in the differential diagnosis of mesenchymal tumours of GI tract. Around 90% to 95% of the GISTs express KIT.[1] They are characterised by diffuse cytoplasmic, membrane or a dot-like perinuclear accentuation pattern. ("Golgi-pattern") (Figure 4)[19] Less than 5% of GISTs are negative for KIT. CD117 is found positive in other tumours like malignant melanoma, synovial sarcoma, desmoids tumour and schwannoma. KIT-negative GISTs have preference for stomach and usually reveal pure epithelioid or mixed cells. and are more likely PDGRFA mutant or KIT wild-type GISTs.[19]

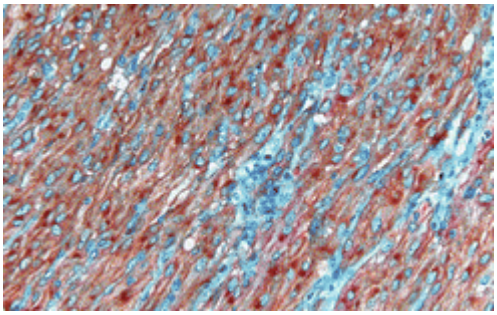


Figure 4: DOT like pattern of KIT expression.

DOG1 is another useful marker expressed in GIST. Studies have shown that the sensitivity of this marker ranges from 75% to 100% depending on the type of antibody used. There are two antibodies called as DOG1.1 and clone K9 DOG1. The sensitivity clone K9 DOG1 antibody is higher in detecting both KIT-positive and KIT-negative tumours.[19] In addition, these antibodies are capable of distinguishing tumours with spindle cells and epithelioid cells.

CD 34 is expressed in 60-70% of GISTs. Gastrointestinal leiomyomas and schwannomas are negative for CD34, thus this marker helps in differentiating GIST from both of them. Moreover, CD34 in combination with CD117 and S100 can be used to distinguish GIST from most other mesenchymal tumours.[25] Therefore, a panel of markers are necessary for the diagnosis of GISTs.

Differential Diagnosis

Leiomyomas and leiomyosarcomas are the most commonly mistaken diagnosis for GISTs. These tumours have spindle cell with sausage-shaped nuclei, brightly eosinophilic cytoplasm with defined cell borders. Contrary to spindle cell GISTs, these tumours have more ovoid nuclei and more syncytial appearance.[14] SMA, h-

caldesmon and desmin are expressed in these tumours. Majority of GISTs shows negative staining for desmin.[1]

Mesenteric fibromatosis arises in mesentery and omentum of middle-aged adults, however, it can involve the wall and/or lumen of the gut, like GIST. It is morphologically characterised by long sweeping fascicles of fibroblastic/myofibroblastic spindle cells set within a collagenous matrix. IHC reveals that desmoid tumours are negative for CD34 and CD117. It shows SMA and desmin positivity.[3] About 70% of these cases shows a strong nuclear staining for beta-catenin whereas it is negative in GISTs.[14]

Gastrointestinal schwannomas are benign tumours that occur in the stomach or colon. It is very important to observe the tumour under low-power these tumours often have sprinkled lymphocytes and a nodular lymphoid cuff. They also express S100 and as exhibit positive staining with glial fibrillary acidic protein.[3]

Inflammatory myofibroblastic tumours mainly occur in children and young adults and more commonly involve mesentery. IHC shows positivity for anaplastic lymphoma kinase (ALK-1), an important diagnostic marker for this tumour.[19]

Tumour site

Most oesophageal GISTs are diagnosed at advance stage and have a poor clinical outcome.[27] GISTs arising from stomach have favourable outcome, whereas the reverse is true in the intestine. Approximately 66 % of all GISTs arise in the stomach and have a better survival rate than small intestinal GISTs of indistinguishable size and mitotic activity. The benign gastric GIST are usually less that 5cm in size and show limited mitotic activity.[27]

Colonic GISTs are too uncommon for statistical analysis, but it is found that they have a benign to malignant ratio of 1:2. All GISTs emerging from the appendix to date were reported to be small, benign tumours and found incidentally. The third most common site for GISTs after the stomach and ileum is rectum. The tumour size less than 2 cm and less than 5 mitoses per 50 HPFs seem to reveal benign behaviour on long-term follow-up. On the contrary, the majority of clinically aggressive rectal GISTs were found to measure more than 5cm or had more than 5 mitoses per 50 hpfs.[27]

Tumour Size and Mitotic Activity

The most dependable prognostic components for GISTs are the size of the tumour and the mitotic activity. The bigger size tumours tend to have worse prognosis than smaller GISTs.[19] Findings of Mienttinen and colleagues show stomach GISTs tend to be less aggressive than intestinal and rectal GISTs.[14] Gastric GISTs tend to be less aggressive than intestinal GISTs, even those tumours with size more than 5cm, provided their mitotic activity is low (no more than 5 mitoses per 50 hpfs) When the tumour size is less than 2 cm and they have less mitotic index (not more than 5/50 hpfs.) these tumours are considered to be benign tumours (Table 1).

Cellularity and Nuclear Atypia

Cellularity is difficult to standardise and its application is specifically problematic in difficult cases. Nuclear atypia is not prominent in GISTs as well as its importance is not clear.[28]

Mucosal Invasion

Mucosal invasion is an uncommon but peculiar feature of a minority of GISTs at various locations. They appear as a diffuse “lymphoma-like” pattern of growth between the glandular elements of the mucosa. Mucosal invasion is present only in malignant GISTs and was identified as a prognostically adverse sign in a few series of duodenal and small intestinal GISTs.[28]

Morphologic Risk Assessment in GIST

The first widely accepted scheme to predict the risk of aggressive clinical behaviour in GIST was published in 2002 by Fletcher CDM et al (Table 1). This scheme does not categorise the tumours as benign or malignant but predicts the chance of aggressive clinical behaviour.

Table 1: Assessment of the risk GISTs based on tumour size and mitotic activity from Fletcher CDM et al.[8]

Risk	Tumour Size	Mitotic Count
Very low risk	< 2 cm	< 5/50 HPF
Low risk	2 – 5 cm	< 5/50 HPF
Intermediate risk	<5 cm 5-10 cm	6-10/50 HPF < 5/50 HPF
High risk	> 10 cm Any size > 5 cm	Any mitotic rate >10/50 HPF >5/50 HPF

Table 2: The risk classification for primary GIST by mitotic index, size and tumor site. Adapted by NCCN from Miettinen et al.[28]

Tumor Parameters		Risk of Progressive Disease [a]			
Mitotic index	**Size**	**Stomach**	**Duodenum**	**Jejenum or ileum**	**Rectum**
≤ 5 per 50hpf	≤ 2cm	None	none	none	None
	> 2 ≤5cm	Very low (1.9%)	Low (8.3%)	Low (4.3%)	Low (8.5%)
	> 5 ≤10cm	Low (3.6%)	Insufficient data	Moderate (24%)	Insufficient data
	> 10 cm	Moderate (10%)	High (34%)	High (52%)	High (57%)
> 5 per 50hpf	≤ 2cm	None [b]	Insufficient data	High [b]	High (54%)
	> 2 ≤5cm	Moderate (16%)	High (50%)	High (73%)	High (52%)
	> 5 ≤ 10cm	High (55%)	Insufficient data	High (85%)	Insufficient data
	> 10 cm	High (86%)	High (86%)	High (90%)	High (71%)
[a] defined as metastasis or tumor-related death [b] denotes small number of cases					
Data based on long term follow up of 1055 gastric, 629 small intestinal, 144 duodenal and 11 rectal GISTs.					

Summary and Conclusion

GIST is a distinct entity by itself with specific histomorphological features. There are various ways to distinguish GIST from other GI tract tumours. IHC (CD117) and other ancillary studies help differentiating GIST and confirm the diagnosis. The deeper understanding of the molecular pathogenesis has established novel treatment modalities. Overall, classification of distinct tumours is important in order to give an appropriate medication to the patient with GISTs.

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