ORIGINAL RESEARCH PAPER
Volume - 15 | Issue - 01 | January - 2026 | PRINT ISSN No. 2277 - 8179 | DOI : 10.36106/ijsr
INTERNATIONAL JOURNAL OF SCIENTIFIC RESEARCH

GASTROINTESTINAL STROMAL TUMOURS (GISTs): AN OVERVIEW OF THE KEY HISTOLOGICAL FINDINGS AND ITS MOLECULAR UPDATES

Oncopathology

Haobijam Persy* Fellowship, Oncopathology, Rajiv Gandhi Cancer Institute and Research Centre (Fellow). *Corresponding Author

ABSTRACT

Gastrointestinal tumour (GIST) is a mesenchymal tumour that can occur anywhere in the GI (gastrointestinal) tract. The most common locations being stomach and small intestine. GISTs account for 2.2% of all malignant gastric tumours. Most cases of GISTs are sporadic while few occur as part of familial syndromes. Over the last decade, there has been an outstanding development in the diagnosis, classification and treatment of GISTs. Vague abdominal pain, bleeding, abdominal mass are the common presentations of GISTs. However, the clinical presentations may vary depending on the size, location and aggressiveness of the tumour. The correct diagnosis of GISTs and its classification is determined by histopathological examination supported by immunohistochemistry. There are three main histological types of GISTs. These are spindle cell type, epithelioid cell type and mixed cell type. The prognosis of patients with GIST depends on a number of factors such as risk category, GIST stage, treatment applied and recurrence after treatment. In this article, I intend to emphasize on the epidemiology, clinical features, diagnosis, classification and treatment modalities of GISTs. A concise discussion regarding the recent molecular biomarkers have also been highlighted in this article.

KEYWORDS

Gastrointestinal stromal tumour (GIST), mesenchymal tumour, histopathological examination

INTRODUCTION

Gastrointestinal stromal tumour (GIST) is a non-epithelial mesenchymal neoplasm. Around 25% of gastric GISTs are clinically malignant.[1] GIST is characterized by differentiation towards the interstitial cells of Cajal. GISTs were originally described as smooth muscle tumours, but the advancements in the diagnostics – immunohistochemical and molecular have led to recognition of GISTs as a distinct category. The use of terminologies such as leiomyoblastoma, gastro pacemaker cell tumour (GIPACT) and gastro autonomic nerve sheath tumour (GANT) are now not recommended. [1,2]

GISTs can occur anywhere in the GI tract. Stomach is the most common site for GIST. Approximately 54% of all GISTs arise in the stomach followed by 30% in small intestine (including duodenum), 5% in colon and 1% in esophagus.[3]

Most cases of GISTs express c-KIT (CD117). 95% of GISTs are positive for c-KIT (CD117) and 5% of these tumours do not express c-KIT. Patients with GISTs can also harbour mutations in the platelet-derived growth factor receptor alpha (PDGFRA) or succinate dehydrogenase complex (SDH). [1,3]

CLINICAL FEATURES

The common presentations of GISTs are vague abdominal pain, bleeding and abdominal mass. However, the clinical presentations may vary depending on the size, location and aggressiveness of the tumour. GISTs present as well-circumscribed mass of variable size ranging from incidental sub-millimetric (microGISTs) lesions to >20cm. [1,4]

Most GISTs are sporadic. Only up to 10% occur in association with a variety of syndromes such as Primary familial GIST syndrome, Carney triad syndrome, Carney-Stratakis syndrome (dyad) and Neurofibromatosis type 1(NF1). [1,2]

HISTOLOGICAL CLASSIFICATION OF GISTs

Microscopically, GISTs has been divided into three main types- spindle cell type, epithelioid cell type and mixed cell type. The histologic appearance is influenced by the anatomic location (gastric vs. small bowel).[1,5]

Spindle cell type: These are the most common histologic type of GISTs (70%). These are composed of tumour cells with elongated spindle-shaped nuclei and abundant eosinophilic fibrillary cytoplasm arranged in diffuse sheets, short fascicles or vague storiform arrangements. Nuclear palisading and perivascular hyalinization can be seen. Tumours with low malignant potential may show deposition of amorphous eosinophilic extracellular collagen globules referred to as skeinoid fibres. [1,3,5]

Epithelioid Cell Type: Epithelioid cell morphology is defined by the presence of round to polygonal cells with a centrally placed nucleus and abundant eosinophilic or clear cytoplasm. Tumors of this type are located mostly in the stomach, and more often negative for c-KIT expression and can harbour PDGFRA mutation. GISTs with SDH-deficiency show epithelioid morphology.[2]

Mixed cell type: Mixed type features a combination of both spindled and epithelioid histology.

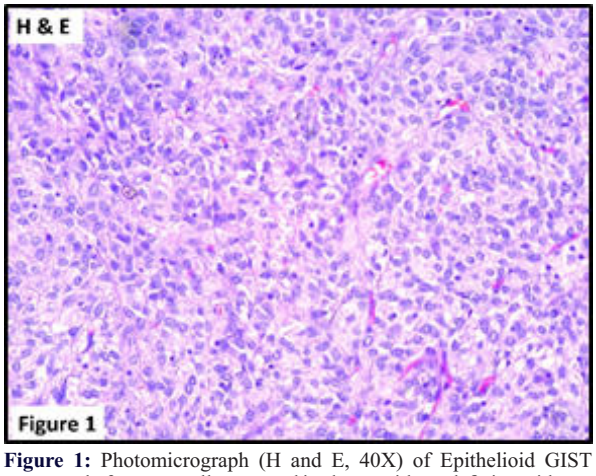

Figure 1: Photomicrograph (H and E, 40X) of Epithelioid GIST composed of tumour cells arranged in sheets without definite evidence of glandular or squamous differentiation. Tumour cells are mildly pleomorphic having round to ovoid vesicular nuclei with variably prominent nucleoli and scant to moderate amount of palely eosinophilic cytoplasm.[3]

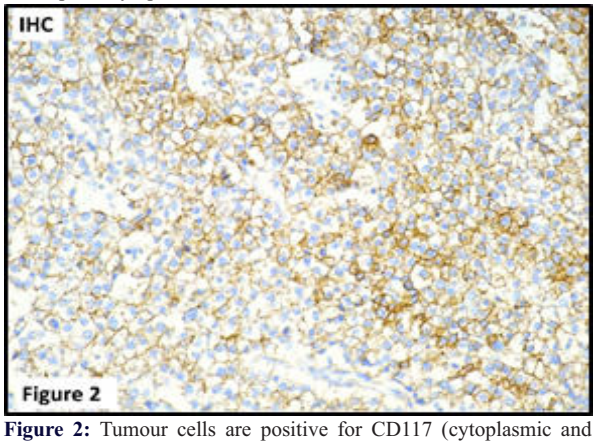

Figure 2: Tumour cells are positive for CD117 (cytoplasmic and membranous).

Immunohistochemistry
Immunohistochemically, the markers that may contribute to the differentiation of GISTs from other subepithelial tumours in the gastrointestinal tract are: KIT (CD117); DOG-1 (discovered on GIST-1) and protein kinase C theta (PKC-theta). Other markers include CD34, smooth muscle actin (SMA), S-100 protein, desmin and keratin. Most GISTs show strong and diffuse expression of c-KIT (CD117). DOG1 may be positive in cases which are negative for c-KIT. DOG1 may be helpful in the diagnosis of as many as 50% of KIT-negative GISTs. Most spindle cell GIST especially of gastric origin are positive for CD34 but epithelioid GISTs are less consistently positive. [1,2,5]

Molecular
Most GISTs harbour gain-of-function mutations of the KIT or PDGFRA oncogenes. Most syndromic genes are caused by germline mutations of KIT or PDGFRA (rarely). About 85% of GISTs have mutations that involves KIT or PDGFRA oncogene.

KIT
KIT is a tyrosine kinase molecule across the cell membrane that acts as a receptor for stem cells. The activation of KIT through its dimerization in turn activates the transduction signal pathway namely RAS-RAF-MAPK and PIK3-AKTmTOR pathways.

About 75% of GISTs harbour gain-of function mutations of KIT involving exon 11(66%) or exon 9(6%) or exons 13 and 17(1% each).

PDGFRA
About 10% of GISTs harbour PDGFRA activating mutations (exon 18: D842V with its significance of resistance to imatinib and non-D842V being sensitive to imatinib; exon 12, and rarely exons 14 and 10). [1,2,6]

The downstream oncogenic signaling involved in PDFRA mutation is similar to that of KIT i.e. PDGFRA mutation involves the RAS/MAPK and PI3K/AKT/mTOR pathways. [1]

A minority of GISTs with PDGFRA mutations may show loss of expression for KIT.

DOG1 (Discovered on GIST)
It is a chloride-channel protein which has a high sensitivity and specificity for diagnosis of GISTs. DOG1 may be helpful in the diagnosis of as many as 50% of KIT-negative GISTs. [1,6]

WILDTYPE GISTs
Wildtype GISTs is a variety of GISTs that do not show KIT or PDGFRA mutations.

There are 2 types of wildtype GISTs:
1. SDH-mutant
2. SDH-deficient

SDH-deficient GISTs
60% harbour inactivating mutations and 40% harbour SDHC promoter methylation leading to SDH dysfunction (~ SDH-deficient GIST). SDH-deficient GISTs characteriscally exhibit/display epithelioid morphology.

SDH-mutant GISTs
Patients with Carneys triad usually show SDHC epimutation. SDHA is the most commonly mutated subunit of SDH gene followed by SDHB, SDHC and SDHD. [1,4]

Treatment Of GISTs
There are 2 treatment options for GISTs. These are:
1. Neoadjuvant therapy and
2. Surgery

SURGERY
The standard treatment of localized GISTs is surgery. Both the tumour and its pseudocapsule should be removed to yield an adequate surgical margin, as the goal in primary GISTs is complete removal (R0). With recent advancements in the use of targeted therapy in the treatment of GISTs, surgical resection still remains the curative treatment for GISTs. [1,2,3]

NEO-ADJUVANT THERAPY
Neoadjuvant therapy is indicated in locally advanced disease, large-sized tumours, tumours which are at not readily accessible sites and in tumours with high-risk of recurrence.

The neoadjuvant drug of choice used for GISTs is Imatinib. Sunitinib and Regoratinib are the second and third line of drugs respectively.

According to ESMO (European Society for Medical Oncology) guidelines, for maximum benefit as a neoadjuvant therapy, Imatinib should be used for a minimum duration of 3-12 months.

PROGNOSIS AND PREDICTION
The parameters that have been best documented for prognosis in GISTs are mitotic rate, tumour size and anatomical site. Mitotic count is done in an area of 5mm2 which in most modern microscopes corresponds to 20–25 fields with the 40× objective and standard eyepiece diameter. The prognostic assessment applies best to KIT/PDGFRA mutant GISTs.

RISK STRATIFICATION
The main aim of risk stratification system is to assess the risk of a poor outcome and to provide a correct road map for the treatment of patients who will benefit from adjuvant therapy such as tyrosine kinase inhibitors (Imatinib). Since all GISTs have the potential for malignancy, multiple consensus has been developed over the years, defining criteria for its stratification based on the risk of metastasis or recurrence. [1,2]

Risk Stratification Systems
NIH Consensus Criteria
Fletcher et al. developed the NIH criteria for GIST. Fletcher used two pathological factors - size of the tumour and mitotic rate. According to NIH, the risk of aggressive evolution is classified into four classes.

Very low risk: tumour size <2 cm; mitotic count <5/50 high-power field (HPF).

Low risk: tumour size 2–5 cm; mitotic count <5/50 HPF.

Intermediate risk: tumour size <5 cm and mitotic count 6–10/50 HPF, or tumour size 5–10 cm and mitotic count <5/50 HPF.

High risk: tumour size >5 cm and mitotic count >5/50 HPF, or tumour size >10 cm and any mitotic rate, or any tumour size and mitotic rate >10/50 HPF. [1,2]

American Forces Institute Of Pathology Criteria
The American Forces Institute of Pathology (AFIP) criteria include the site of tumour in addition to the size and mitotic count as GIST that arises from gastric region are found to have a better prognosis than those arising from other sites of the gastrointestinal tract. [3]

Modified NIH Criteria (Joensuu Risk Criteria)
Joensuu has brought a modification to the existing criteria of NIH system. This modification includes the rupture and location of the tumour. So, this system uses four prognostic factors i.e. tumour size, tumour site, mitotic count and tumour rupture. Tumour rupture is considered as an independent prognostic factor in addition to tumour size, site and mitotic count. [2,3]

CONCLUSION
GISTs are mesenchymal tumours that can occur anywhere along the GI tract. GISTs may occur sporadically, or as part of a familial syndrome. The histogenesis of these tumours is variable. Histopathological and immunohistochemical studies are necessary for distinguishing GISTs from other tumours with same localization. The prognosis of patients with GIST is quite variable and depends on a number of factors, such as risk category, stage, treatment etc. Younger age, higher tumour size, increased mitotic index and tumour location are some of its negative prognostic factors. Gastric tumours have a better prognosis than those found elsewhere in the GI tract. The proper assessment of mutational status is required in patients with GISTs for personalized treatment such as use of Tyrosine Kinase Inhibitors (TKIs). There has been an improvement in the 5 years survival rate, mortality and morbidity in these patients following the advancements in the diagnosis and treatment in the recent years.

REFERENCES
1. WHO Classification of Tumours. Digestive system, tumours, 5th edition, Volume 1.

2. Gheorghe G, Bacalbasa N, Ceobanu G, Ilie M, Enache V, Constantinescu G, Bungau S, Diaconu CC. Gastrointestinal Stromal Tumors-A Mini Review. J Pers Med. 2021 Jul 22;11(8):694. doi: 10.3390/jpm11080694. PMID: 34442339; PMCID: PMC8400825.
3. Singh, Rohit & Tiwary, Satyendra & Puneet, & Khanna, Ajay K. (2022). Gastrointestinal Stromal Tumor: Review. Galore International Journal of Health Sciences and Research. 7. 7-18. 10.52403/gijhsr.20220102.
4. Parab TM, DeRogatis MJ, Boaz AM, Grasso SA, Issack PS, Duarte DA, et al. Gastrointestinal stromal tumors: a comprehensive review. J Gastrointest Oncol. 2019;10(1):144–54
5. Ma GL, Murphy JD, Martinez ME, Sicklick JK. Epidemiology of gastrointestinal stromal tumors in the era of histology codes: results of a population-based study. Cancer Epidemiol Biomarkers Prev. 2015;24(1):298–302
6. Tryggvason G, Gíslason HG, Magnússon MK, Jónasson JG. Gastrointestinal stromal tumors in Iceland, 1990-2003: the icelandic GIST study, a population-based incidence and pathologic risk stratification study. Int J Cancer. 2005;117(2):289–93