Gastrointestinal stromal tumours (GIST) revisited

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Introduction

Gastrointestinal stromal tumours (GIST) are defined as mesenchymal neoplasms expressing CD 117 (a protooncogene protein). They are now considered as biologically discohesive tumours which should be distinguished from muscle tumours (leiomyoma and leiomyosarcoma) and neural tumours (Schwannoma) of the gastrointestinal tract. They are the most common mesenchymal neoplasms of the gut.

In the past there has been much confusion regarding this subject. The constantly changing nomenclature, incomplete understanding of the histogenesis, lack of a typical immunophenotype and difficulty in predicting the biological behaviour in terms of traditional histological parameters have been some of the issues that have brought about this confusion among pathologists.

However over the last decade the identification of mutations of the gene encoding c-kit in many GISTs has resulted in a better understanding of the histogenesis and refinement of the diagnostic criteria for GISTs. The finding of the anti-tumour effects of the molecular inhibitor Imatinib ([Gleevec]: Novartis Basel Switzerland) has been a remarkable clinical breakthrough as these tumours have been resistant to conventional chemotherapy.

This article reviews the epidemiology, clinical presentations and pathology of these tumours with emphasis on the emerging concepts regarding GISTs and their impact on our understanding of these tumours.

Historical overview and the evolution of current nomenclature

In 1941 Stout and co-workers described leiomyoma, leiomyosarcoma, leiomyoblastoma and bizarre leiomyoma of the gastrointestinal tract (1). Since then spindle cell tumours of the gastrointestinal tract were considered as being of smooth muscle origin, due to the site of origin within the muscularis propria and the histologic resemblance to smooth muscle. However electron microscopic studies in the late 1960's (2) and immunohistochemical studies in the 1980's (3) showed that these tumours lacked convincing evidence of smooth muscle differentiation.

It was also noted that some cases of these stromal neoplasms showed immunohistochemical and ultrastructural evidence of schwannian and neuroaxonal differentiation. A subset of spindle cell tumours of the gastrointestinal tract showing autonomic neuronal differentiation were designated by Herra et al in 1984 as plexosarcoma (4) and subsequently as Gastrointestinal autonomic nerve tumour (GANT) (5).

The confusing array of acronyms included STUMP (stromal tumours of uncertain malignant potential), GANT (gastrointestinal autonomic nerve tumour) and most recently GIPACT (Gastrointestinal pace maker cell tumour) and the more generic term 'stromal tumours' introduced by Mazur & Clark in 1983 (6).

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By the early 1990's there was much confusion regarding the histogenesis of these tumours with two approaches being adopted to solve this dilemma.

The first was to include all mesenchymal tumours under the umbrella term of GIST irrespective of immunophenotypic or ultrastructural evidence of these being smooth muscle or neural tumours. The second approach was to exclude true leiomyomas and schwannomas, from the definition of GIST based on immunophenotypic and ultrastructural evidence.

Though the second approach was closer to the

current thinking on GISTs it was beset by problems such as lack of reproducibility and the lack of a sensitive and specific diagnostic marker that could reliably exclude smooth muscle and neural tumours. The expression of CD 34 by many GISTs suggested a specific entity different from smooth muscle tumours.

The subsequent discovery of kit protein (CD117) expression by these tumours has however brought about a more clear definition of GIST.

A comparison of the previously used diagnostic terminology and the currently accepted terminology is set out in Table 1.

Table 1. Comparison of previous terminology and current terminology in regard to GISTs

Previous terminology	Current terminology
Oesophageal leiomyoma	Most are leiomyomas, histologically and clinically separate from GISTs
Gastric leiomyoma	Majority are GISTs. Very few are leiomyomas similar to those more commonly seen in the oesophagus.
Gastric Leiomyoblastoma	Correspond to epithelioid GIST
Gastric Leiomyosarcoma	Great majority are GISTs.
Small intestinal leiomyoma and leiomyosarcoma	Great majority are GISTs
Colonic and rectal leiomyoma	The small tumors involving only the muscularis mucosae are true leiomyomas. Some tumours externally involving colon and rectum in women are uterine-type leiomyomas with oestrogen and progesterone receptor positivity. Most intramural tumors are GISTs and very few are true leiomyomas.
Colonic and rectal leiomyosarcoma	Great majority are GISTs. Small minority are true leiomyosarcomas.
Gastrointestinal autonomic nerve (GANT)	This category merges with GIST representing an ultrastructural variant.
Leiomyoma / Leiomyosarcoma of omentum and mesentry	A majority of tumors are GISTs and a minority are leiomyosarcomas.
Retroperitoneal leiomyosarcoma	Includes up to one third of GISTs - primary from the stomach or intestines, omentum, mesentery and retroperitoneum. Clinical and gross pathology correlation are needed for determination of primary site.

Definition of GIST

At present, GIST is defined as a cellular, spindle cell, epithelioid cell or occasionally pleomorphic cell, mesenchymal tumour of the gastrointestinal tract that expresses kit (CD117 – stem cell factor receptor) protein as detected by strong and uniform staining using immunohistochemical methods. The majority of GI mesenchymal tumours are GISTs.

It must be reiterated that this definition excludes all true GI smooth muscle tumours (leiomyomas and leiomyosarcomas) and neural tumours (schwannoma and neurofibroma).

The problem is however that of a small group of tumours which are histologically similar to GIST's with no evidence of myoid or neural differentiation, not expressing kit and lacking in all other markers used in the diagnosis of GIST such as CD34. This group is difficult to define or classify in the present context - though some authors do believe that these tumours probably belong to the group of GISTs showing a 'null' phenotype. Further morphological and molecular genetic studies are necessary to determine whether or not they belong to the GIST group.

Epidemiology

According to population based studies the estimated incidence of GISTs is around 10 – 20 per million and of these 20 – 30% are malignant (2). However some of these figures on the incidence of GISTs may be misleading as some of the larger studies included true smooth muscle and neural tumours and did not adhere strictly to the definition of GIST as given above.

GISTs typically occur in older individuals over 50 years of age ranging between 55 - 65 years. GISTs are rare before the age of 40 years and are very rare in children (7). Some series report a male preponderance while others show an approximately equal sex distribution (7,8).

Most GISTs are found in the stomach and small intestine, accounting for 50 – 60 % and 30 – 40% respectively. About 10% affect the rectum and 5%

the colon, while isolated cases have been reported in other intra abdominal sites such as mesentery, omentum, retroperitoneum and appendix (9).

Clinical presentation

Small GISTs are often found incidentally on the gastric or small intestinal serosa during surgery or in a specimen removed for other conditions. They may also be detected incidentally during radiology or gastroscopy as a submucosal nodule or on per rectal examination.

Symptomatic GISTs in the oesophagus present with dysphagia or as a mediastinal tumor that is at surgery noted to be connected with the oesophagus (10). Gastric and small intestinal GISTs present with vague symptoms but sometimes cause upper GI bleeding (8). Colonic GISTs may manifest with GI bleeding, colonic perforation, pain, obstruction or as a combination of these features (8). Large intra abdominal tumours may be palpable extra abdominally and some patients may present with liver metastases.

In rare instances GIST's occur as a part of tumour syndromes. These being Carney's triad which includes GIST, paraganglioma, and pulmonary chondroma described by Aidan Carney, an endocrine pathologist (11) and in connection with Neurofibromatosis Type 1 syndrome (12).

Pathology

Macroscopically tumours vary in size ranging from 1 – 2cms to more than 20cms in diameter. They are well circumscribed and though unencapsulated a pseudocapsule may occasionally be seen. The tumours could be submucosal (with or without overlying mucosal ulceration), intramural or subserosal in location (2,3).

Microscopically the GISTs are composed of spindle cells (60-70% of cases), epithelioid cells (30-40% of cases) or combination of both in variable proportions (2,3). Spindle cell GISTs (Figure 1) are composed of uniform eosinophilic cells arranged in short fascicles or whorls. Tumour cells have pale eosinophilic cytoplasm with a fibrillary and syncytial appearance

(with indistinct margins) and the nuclei tend to be uniform more ovoid and shorter with vesicular chromatin in comparison with smooth muscle tumours. Prominent nuclear pleomorphism is unusual in GISTs. In 5 % of cases cytoplasmic juxtanuclear vacuoles may also be present. Nuclear palisading and microcystic stromal degeneration present in GISTs are reminiscent of neural tumours. Stromal lymphocytes and haemorrhages may be present. Stromal collagen tends to be minimal.

GISTs of epithelioid type (Figure 2) are composed of rounded cells with variably eosinophilic or clear cytoplasm. In some cases with clear cytoplasm the presence of "retracted" eosinophilic cytoplasm can be seen around nuclei simulating inclusions. Epithelioid lesions too show a uniform round – ovoid nucleus with vesicular chromatin (2,3) Some GISTs may reveal a paraganglioma or a carcinoid like, nested or organoid architectural pattern.

Approximately 10 – 20% of the cases of both spindle and epithelioid type GISTs, and most of those arising in the intestine exhibit stromal skenoid fibres (2,3). Though previously thought to signify neural differentiation these have no histogenetic significance. They are hyaline, fibrillary, brightly eosinophilic structures, composed of nodular tangles of collagen fibres (13). They are PAS positive and diastase resistant.

Immunophenotype

Uniform positivity of CD117 staining has been demonstrated in GISTs irrespective of cytomorphology (14) and is now the gold standard of diagnosis of GISTs, especially since CD117 is not expressed by tumours of smooth muscle and neural origin which prove to be the most important entities in the differential diagnosis of GIST. It is however not tumour specific and is expressed by many normal cells of the gastrointestinal tract which often act as positive internal controls in immunohistochemically stained sections, but should not be confused as focal positivity in an otherwise negative mesenchymal tumour.

Many other extra gastrointestinal tumour cells also exhibit CD117 positivity. (See Table 2 adapted from Chan (15)).

Another immunohistochemical marker which has proved useful is CD34 (My10, QBEND 10) which is a haemopoietic progenitor cell antigen present in subsets of fibroblasts and many other neoplasms (16) (See Table 3).

60 – 70% of GIST's show positivity with CD34 (14). However this antigen is also expressed by some smooth muscle tumors and is therefore not specific (Table 3).

About 20 - 40% of GISTs show focal reactivity for smooth muscle actin, less than 2% express desmin and less than 5 % stain for S100.

Figure 1. Spindle cell GIST H&E X 400

Figure 2. Epithelioid GIST H&E X 400

Table 2. Normal and neoplastic tissue that express CD117/c-kit

Normal tissue	Neoplastic tissue
Gastrointestinal tract Interstitial cells of Cajal Mast cells	Gastrointestinal tumours Gastrointestinal stromal tumours.
Extra gastrointestinal sites A subset of CD34 positive haemopoietic stem cells. Melanocytes Basal cells of epidermis Immature Langerhan cells in epidermis. Epithelial cells – salivary gland, sweat gland, renal tubules Cells in reproductive system Subset of glial cells. Osteoclast precursors	Extra gastrointestinal sites Anaplastic large cell lymphoma Acute myeloid leukaemia Reed-Sternberg cells in Hodgkin's lymphoma Melanoma (loss in vertical growth and metastases) Endometrial carcinoma, Germinoma Glioma Clear cell sarcomas of tendon sheaths and aponeuroses. Ewing's sarcoma group Anaplastic small cell carcinoma of the lung. Mastocytosis.

Table 3. CD 34 positive tumours

Gastrointestinal tumours	Extra gastrointestinal tumours
Gastrointestinal stromal tumours	Non-gastrointestinal smooth muscle tumours Solitary fibrous tumour Dermatofibrosarcoma protruberans. Kaposi's sarcoma Lipoma/ angioliipoma/spindle cell lipoma/atypical lipoma. Neurofibroma Vascular tumour Epithelioid sarcoma.

Ultrastructure

Electron microscopy has provided some clarification of the range of cellular differentiation seen within this group of tumours (5,15,17). Well developed myofilaments are not present as is the case for well developed focal densities and attachment plaques which therefore indicate the presence of only incomplete myoid differentiation.

Complex cytoplasmic extensions, neurite – like processes, microtubules and synapse like structures and dense core granules on the other hand indicate variable neural differentiation in some of the GISTs. In each of the above cases the ultrastructural features correlate with the immunoprofile substantiating the presence of myogenic or neural differentiation albeit incomplete.

Prediction of biological behaviour

Throughout the years many parameters have been evaluated in order to establish criteria for malignancy or the potential to metastasize.

Mitotic activity (18,19), tumour size (19,20,21) tumour necrosis (19) histological type or pattern (22), immunohistochemical staining for proliferation antigens and ploidy status (18,19,21) are some of these parameters assessed. The morphological features that have gained the most acceptance as being predictive of the biological outcome of these tumours are mitotic activity and tumour size.

Even small tumours (<2.0cms in size) with very low mitotic activity (<5/50 High power fields) occasionally metastasize.

Thus it would be more appropriate to adopt the approach of risk assessment (Table – 4) as proposed by Fletcher et al (3) rather than categorize GISTs into benign or malignant categories. All patients with GISTs should be carefully and regularly followed up for an indefinite period, in view of the small number of cases that behave in an unpredictable manner (3).

Differential diagnosis

It has become very important to identify GISTs because of the availability of kit tyrosine kinase inhibitor imatinib (STI –157) which has shown promising clinical results in the treatment of GISTs (23,24). The tumours that bear a histological resemblance to GISTs and the features that distinguish them from GISTs are presented in Table 5.

The tumours that are CD117 positive which are listed in Table- 2 present the practising histopathologist with very little diagnostic problems when the proper clinical setting is taken into account. The only rare occasions this may prove to be diagnostically problematic are in cases of metastases of GIST to the liver, soft tissue or in GISTs arising in the retroperitoneum.

Role of kit protein in histiogenesis, diagnosis, prognosis and treatment.

The kit protein (CD117 antigen, in the standardized terminology of cluster of differentiation of leukocyte antigens) is a transmembrane growth factor receptor for stem cell factor (SCF) also called SCF – receptor. This 145 – 160 KDa gene product is a transmembrane tyrosine kinase receptor displaying extensive homology with other members of the tyrosine kinase receptor family, such as platelet-derived growth factor receptor (PDGFR), and colony-stimulation factor-1 (CSF-1). Kit consists of an extracellular region, a single membrane spanning region and a cytoplasmic region.

There is evidence that activation of kit by its ligand SCF is critical for diverse mast cell functions including proliferation of cells, chemotaxis and cytoskeletal rearrangement (25).

In 1998 Hirota and colleagues reported (26) that some GISTs contained an exon 11 (juxtamembrane domain) mutation in the c-kit protooncogene. This was then recognized as being a central event in the pathogenesis of GIST and has subsequently been demonstrated in about 50% of cases of GISTs. Several other genetic changes including mutations in the extracellular domain (exon 9) and kinase domain (exon 13) of kit have been documented (27).

It has been shown that GISTs share a phenotypic similarity with the kit positive interstitial Cajal cell of the GI tract.

These cells function as pacemaker cells that regulate autonomic intestinal motility, their development depends on cellular signalling regulated by the kit protein and show capability of differentiating into smooth muscle if deprived of kit signalling. This and other experimental data strongly suggest that Cajal cells or their subsets represent a multipotential stem cell like population, which is the logical candidate for GIST histogenesis (28). Hence the term gastrointestinal pacemaker cell tumour (GIPACT).

Table 4. Approach for defining risk of aggressive behaviour in GISTs

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

Table 5. Differential diagnosis of GIST

Tumour entity	Distinguishing features
Oesophageal leiomyoma	Actin and desmin positive smooth muscle cells. Less cellular than GIST. Occurs more often in younger patients.
Pericolonic leiomyoma	Occurs in women. Histologically similar to uterine leiomyoma. Positive for oestrogen and progesterone receptors, actin and desmin.
Leiomyosarcoma	Rare (10%). Polypoid intraluminal masses. Phenotypic features of well differentiated smooth muscle.
Glomus tumour	Occurs almost exclusively in the stomach.
Inflammatory fibroid polyp	Occurs especially in children and adults.
Mesenteric desmoid	Fibroblasts and myofibroblasts in a collagenous background. CD34 negative.
Solitary fibrous tumour	Peritoneal surfaces – mainly of the liver. Collagenous spindle cell tumour.
Schwannoma	Small, yellow, circumscribed submucosal tumour mostly in stomach and then in colon. Slender spindle cells. S100 and neural markers positive. GFAP positive. (never occurs in GIST)
Undifferentiated Sarcoma	More nuclear pleomorphism than GIST. Do not express any specific cell type markers and cannot be further defined.
Dedifferentiated liposarcoma	Mesenteric and retroperitoneal tumours that involve the intestinal walls simulating GIST. Diagnosis difficult if no adipose tissue is present in the areas sampled.
Metastatic melanoma	Positivity for melanocytic markers (tyrosinase, melan A, HMB45).

The entire definition of GIST is now dependant on the demonstration of kit protein. Hence it's importance in the diagnosis. This has been discussed in detail in the previous sections. A prognostic significance for c-kit mutations was suggested by several clinicopathological studies (29,30), though these need further clarification.

The discovery of the remarkable antitumour effect of the molecular inhibitor STI-571 (Imatinib [Gleevec]: Novartis, Basel Switzerland) has revolutionized the treatment of inoperable and metastatic GISTs. This agent selectively inhibits the ABL, BCR-ABL, KIT, and PDGFR tyrosine kinases. STI-571 is therefore a targeted therapy directed against the apparent fundamental and critical pathogenetic defect in GIST. This treatment therefore is a prototype of a specific inhibitor altering the survival of a neoplastic cell (23).

Further questions to be answered

Although GIST has been recognized as a distinct tumour entity for many years, it is only within the last few years that it has been defined and diagnosed with precision. Though much of the issues that have caused considerable confusion to pathologists the world over have been to some extent resolved there are yet many issues that require clarification such as

1. The classification of the small albeit definite group of mesenchymal tumours of the GI tract that demonstrate a 'null' phenotype.
2. The significance of the different types of kit mutations in the pathogenesis of GIST and their biological behaviour.

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