Special Article

Gastrointestinal Stromal Tumors (GISTs): A Pathology View Point

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Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal tumors of the digestive tract. Most gastrointestinal soft tissue neoplasms, previously classified as leiomyomas, schwannomas, leiomyoblastomas, or leiomyosarcomas, are now classified as GISTs based on histology, immunohistochemistry, and molecular study. They originate from the stem cells that differentiate toward the pacemaker cell (Interstitial cell of Cajal). Prognostic factors have been identified for GISTs and include tumor size and mitotic rate. Surgery is the standard treatment for resectable GISTs. Metastatic and inoperable GISTs should be considered the medication with tyrosine kinase inhibitor (imatinib mesylate), which inhibits the c-kit receptor. The role of the pathologist in the differential diagnosis of GISTs, as well as in the assessment of the malignant potential of the tumors, is becoming increasingly important in influencing decisions regarding clinical management of GISTs. The present paper reviews the literature of GISTs and emphasizes on the field of the pathologist's work.

Keywords: Gastrointestinal stromal tumors (GISTs), c-kit, CD117, Tyrosine kinase inhibitor, Imatinib mesylate

Gastrointestinal stromal tumors (GISTs) are rare tumors of the gastrointestinal (GI) tract, and less frequently, they can be found in mesentery and omentum. They are the most commonly found tumors of mesenchymal tissue origin in the GI tract, comprising approximately 1% of all GI tumors (5% of all sarcoma)[1]. The incidence is currently thought to be approximately 10 to 20 cases per million. The median age at diagnosis is between 55 and 65 years[2]. GISTs are occasionally found in young adults, but they are very rare in children. Most of the data reveal similar frequency in both sexes. The majority of GISTs (40-70%) are found in the stomach, 20-40% are found in the small intestine, 5-15% in the colon and rectum, and < 5% in the esophagus[1]. Approximately 20-30% are malignant at the time of initial diagnosis with the criteria of metastasis and adjacent organs invasion.

Mazur and Clark first described the term GIST in 1983 after studying 28 cases of gastric leiomyomas or leiomyosarcomas. This designation defined as gastrointestinal non-epithelial neoplasms that lacked

the immunohistochemical features of Schwann cells (S-100 protein) and did not have the ultrastructural features of smooth muscle cells[3].

Kindblom concluded in 1998 that GISTs show striking ultrastructural and immunophenotypic (strong and homogeneous immunoreactivity for the kit receptor) similarities with interstitial cells of Cajal (ICC) and that they may originate from stem cells that differentiate toward a pacemaker cell phenotype[4]. Sakurai also supported this hypothesis with a report in 1999, which concluded that both GISTs and ICC expressed the embryonic form of the heavy chain of non-smooth-muscle myosin[5]. Miettinen explained in 1999 that the occurrence of KIT protein-positive tumors outside the gastrointestinal tract (primary in the omentum and mesentery) with similar histology to GIST support the precursor-cell hypothesis[6]. Reith described the same idea in 2000 with the retroperitoneal tumor[7].

Gain-of-function mutations of c-kit (KIT) proto-oncogene in human GISTs that were discovered by Hirota in 1998 are critical to the pathogenesis and have been shown to be associated with malignant behavior and poor survival[8-10].

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Clinical presentation

The symptoms of GISTs depend on tumor size and site of presentation[11]. Many small GISTs (usually less than 2 cm) are incidentally detected upon cancer surveillance (endoscopy or laparotomy), surgery for an unrelated condition, or during imaging examinations. This incidental diagnosis is 40% of cases reported by Nishida in 2004. The most common symptoms of gastric GISTs are vague upper abdominal discomfort or pain (50-70%) and GI bleeding (20-50%)[12]. The small intestinal GISTs may present with pain, bleeding, or signs of obstruction. Duodenal GISTs occasionally cause obstructive jaundice. Nishida also reported the third most common symptom with palpable abdominal mass that are likely to be malignant[13]. The other symptoms are nausea, vomiting, dysphagia (esophageal tumor), appetite loss, weight loss, bowel perforation, and fever. Some patients present with metastatic disease. Liver metastasis (probably results from hematogenous spreading via portal vein) is more frequent than peritoneal surface, lymph nodes, and extra-abdominal sites[11]. Recurrent GISTs have local recurrence (76% with synchronous liver metastasis in a half of cases), solely metastatic liver (15%), and peritoneal metastasis (7%)[14]. The data of the first recurrence has no extra-abdominal metastasis.

The diagnosis of GISTs may be suggested after gross examination during surgery. However, it always requires histological and immunohistochemical confirmation.

Gross findings[12,15,16]

The tumors vary greatly in size, ranging from 1-2 cm to more than 20 cm in diameter. Small GISTs often form solid subserosal, intramural, or less commonly polypoid intraluminal masses. Larger GISTs form external, sometimes pedunculated masses attached to the outer aspect of the gut involving the muscular layers. The tumors are usually well circumscribed and generally unencapsulated, although a pseudocapsule may occasionally be seen. The submucosal lesions may have ulceration of the overlying mucosa.

The cut sectioning has various colors from grey/white to red/brown, depending on the degree of hemorrhage, and may be solid, partially cystic, or necrotic. Larger lesions frequently have central necrosis and may rupture at the time of surgical resection because of friable tumors. Central cysts are also present in larger lesions.

Histologic findings
Cells[1,12,16-18]

Even though Strickland separated cell types into spindle, round (epithelioid), plasmacytoid, myxoid, signet ring, granular, and multinucleated but when prognostic criteria was considered, only spindle and epithelioid cells were mentioned. The other reports classified into three major categories: spindle cell type, epithelioid type, and mixed spindle and epithelioid cell type (in variable proportions) (Table 1, Fig. 1). Strickland also described tumor cells with plasmacytoid, myxoid, signet ring, granular, and multinucleated features.

Nuclear features of GISTs are highly variable, ranging from a monotonous predominantly oval/spindly appearance to obviously pleomorphic. They contain nucleoli of variable prominence and multinulceation may be seen but is not a prominent feature. Mitotic activity may be absent or high. Inflammatory response is variable and composed mainly of lymphocytes and plasma cells. Hemorrhage and necrosis may be present. The prominence of a vascular network is variable. In approximately 10% to 20% of cases, hyaline or fibrillary brightly eosinophilic structures know as

Table 1.

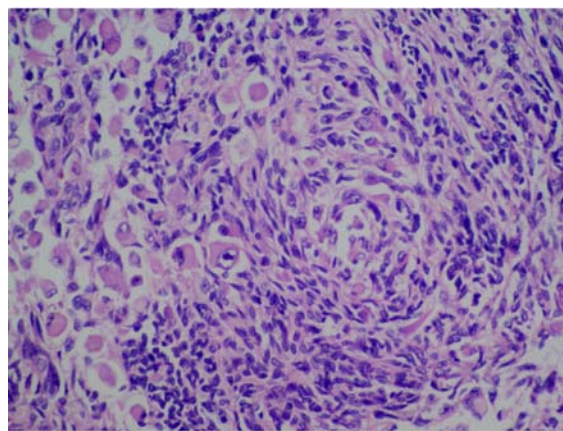| Cell type	Joensuu[1]	van Roggen[16]	Blay[18]
Spindle cell type	70%	60-70%	70%
Epithelioid type	30%	30-40%	20%
Mixed cell type			10%

Fig. 1 The distinction between epithelioid type (left) and spindle cell type (right) (x200, H&E)

skeinoid fibers can be seen. These structures appear to be composed of nodular tangles of collagen fibers and typically exhibit periodic acid-Schiff (PAS) positivity.

When specific cell type is considered, GISTs of spindle cell type tend to have light eosinophilic cytoplasm with occasional basophilic, or amphophilic with a somewhat fibrillar appearance. They usually have compact and high cellularity with fascicular and short storiform pattern. They also have patternless, whorled, or palisading architecture and minimal tumour stroma. The cells usually have indistinct cell borders with oval-shaped and uniform nuclei with vesicular chromatin. Cystic degeneration or stromal hemorrhage may be prominent.

GISTs of epithelioid type tend to have more abundant cytoplasm, ranging from predominant eosinophilic (oncocytic) to amphophilic or clear with well-defined cell borders. They have more frequent nested growth pattern or fascicular appearance than the other patterns found in spindle cell type. They can compose of round-shaped cells with round-to-ovoid nuclei and vesicular chromatin. Cytoplasmic glycogen with a perinuclear distribution is regularly present (Table 2).

GISTs of mixed cell type may have abrupt transition between spindle cell and epithelioid areas or the two cell types are intermingled.

Pattern

The architectural growth patterns may be fascicular, storiform, palisading, diffuse sheet-like, organoid (nested), myxoid, inflammatory, and alveo-lar[17]. GISTs of specific location can be described as the following[19]:

In general, gastric GISTs have distinct histologic subtypes. Most small intestinal GISTs are composed of spindle cells and nearly half of them usually contain round, oval, or elongated eosinophilic and PAS positive aggregates of extracellular collagen fibers (skeinoid fibers). Most GISTs of sites other than stomach and small intestine are spindle cell tumors.

Stomach

Subclassification of the two major cell types (spindle cell and epithelioid) into eight patterns by Miettinen are the following:

Sclerosing spindle cell GISTs (Fig. 2) are paucicellular tumors in collagenous with occasional calcific background. Tumor cells are usually small with low mitotic rate. Palisading-vacuolated spindle cell GISTs (Fig. 3) are the most common subtype among gastric GISTs. They have palisading nuclei, prominent perinuclear vacuolization, and low mitotic rate. Hypercellular spindle cell GISTs (Fig. 4) have densely packed, uniform spindle cells lacking significant atypia and mitotic activity. Sarcomatous spindle cell GISTs (Fig. 5) have marked mitotic activity (> 4 per 10 HPFs) and diffuse atypia (enlarged nuclei and hyperchromasia) with slight pleomorphism.

Sclerosing epithelioid GISTs (Fig. 6) have syncytial polygonal tumor cells in a variably sclerosing stroma with indistinct cell borders. Focal atypia and multinucleation is common but mitotic rate is low. Dyscohesive epithelioid GISTs (Fig. 7) have epithelioid cells with sharp cell borders. Even though focal nuclear

Table 2.

Cell type	Cell	Nuclei	Cytoplasm	Pattern
Spindle cell type	- Spindle shape - Indistinct cell borders	- Oval-shaped and uniform nuclei with vesicular chromatin	- Light eosinophilic (basophilic, amphophilic) - Fibrillar	- Compact and high cellularity with fascicular and storiform pattern - Patternless, whorled, palisading - Minimal tumor stroma
Epithelioid type	- Round-shaped - Well defined cell borders	- Round-to-ovoid nuclei with vesicular chromatin	- Abundant cytoplasm - Eosinophilic (oncocytic) to amphophilic or clear - Cytoplasmic glycogen	- Nested or fascicular

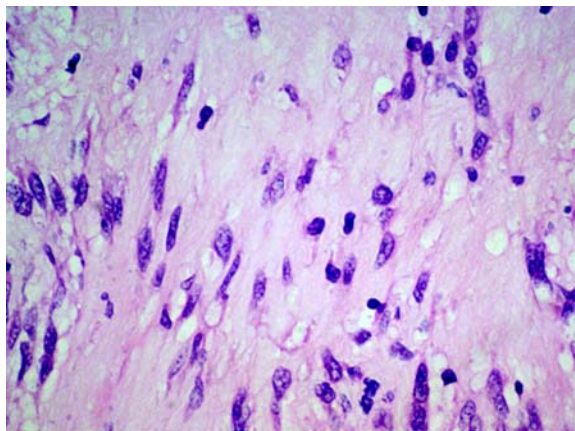Adapted from van Roggen[16] and Blay[18]

Fig. 2 Sclerosing spindle cell GISTs (x400, H&E)
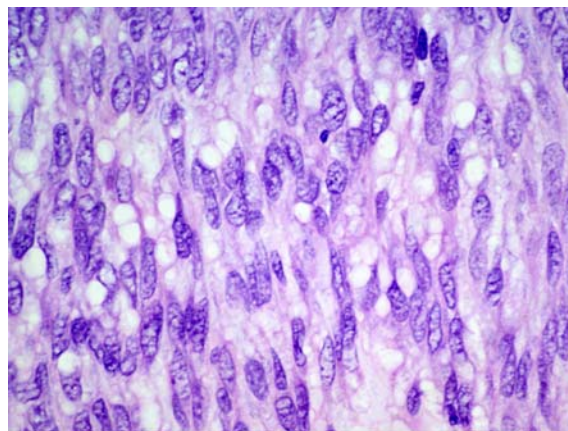

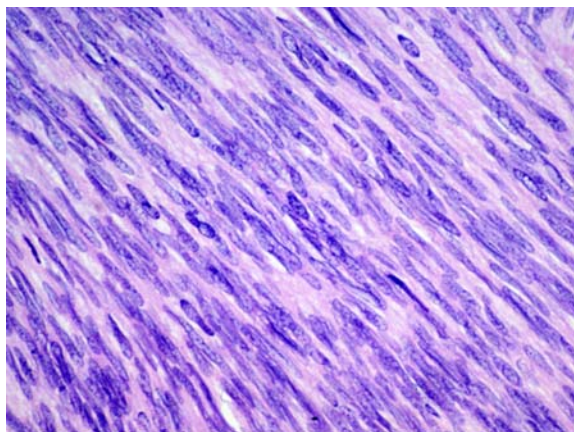**Fig. 3** Palisading-vacuolated spindle cell GISTs (x400, H&E)

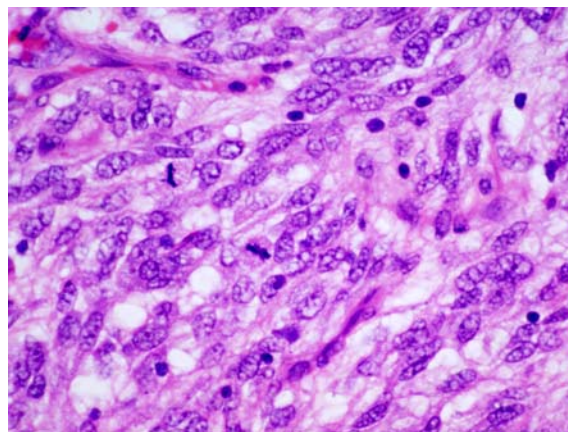**Fig. 4** Hypercellular spindle cell GISTs (x400, H&E)

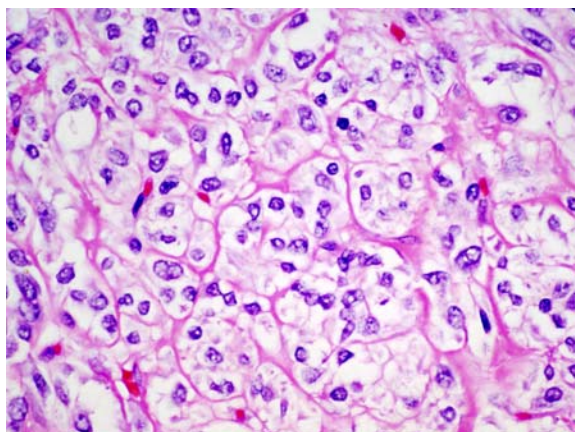**Fig. 5** Sarcomatous spindle cell GISTs (x400, H&E)

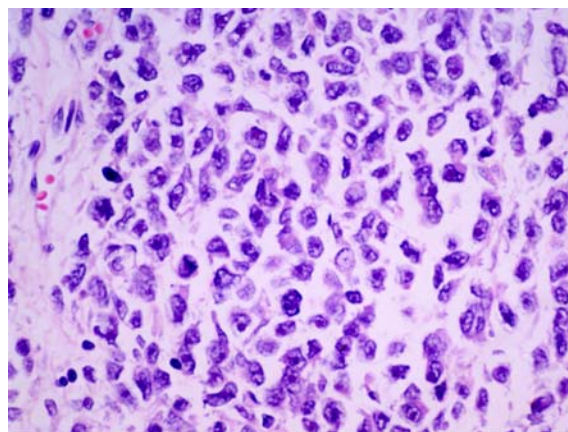**Fig. 6** Sclerosing epithelioid GISTs (x400, H&E)

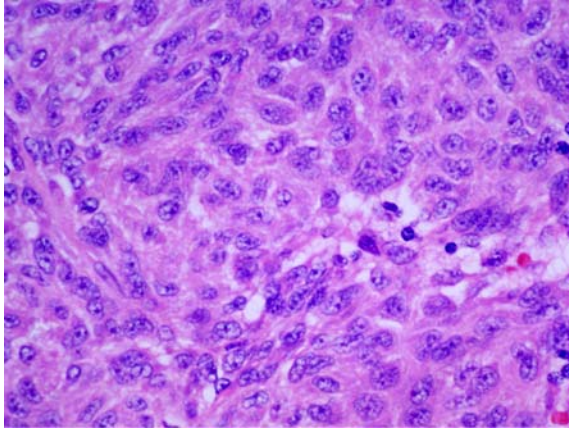**Fig. 7** Dyscohesive epithelioid GISTs (x400, H&E)

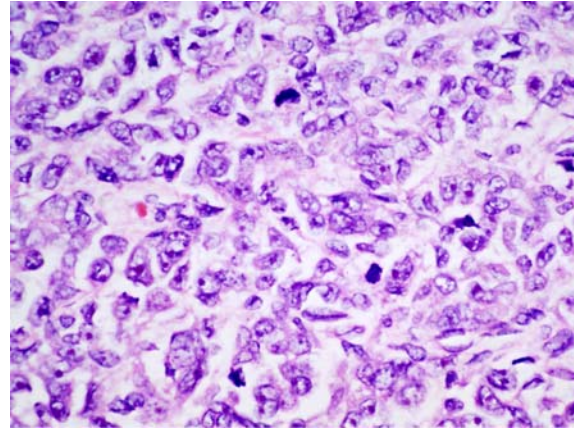**Fig. 8** Hypercellular epithelioid GISTs (x400, H&E)

Fig. 9 Sarcomatous epithelioid GISTs (x400, H&E)

pleomorphism is common, these should be considered when high mitotic rate is present. Hypercellular (Fig. 8) and sarcomatous epithelioid GISTs (Fig. 9) have highly cellular tumors with closely apposed cells and well-defined cell borders. The former has low mitotic rate but the latter has high mitotic rate (often more than 20 per 50 HPFs).

The distribution of GISTs in the stomach is as follows: 40% of pars media, 25% of antrum, 20% of pylorus, 60% of submucosa, 30% of subserosa, and 10% of intramural[17].

Small intestine

Even though malignant tumors occur with increasing frequency in the distal small bowel, predominantly in the ileum but GISTs are uncommon. They have predominant spindle cells with organoid pattern and frequent skeinoid fibers. The other pattern includes anuclear areas resembling neuropil material (collection of entangled cell process). Only a minority of small intestinal GISTs have histologically sarcomatous features with high mitotic activity and pleomorphic forms are rare. Epithelioid GISTs is linked with malignant course and probably represents tumor progression rather than a distinct histologic subtype in the stomach.

Colon and rectum

Most of GISTs have spindle cells and skeinoid fibers are seen in some colonic but not in rectal GISTs. Rectal spindle cell GISTs can show hyalinized-calcified or palisading nuclear pattern and malignant examples can have a leiomyosarcoma-like fascicular pattern.

Epithelioid GISTs are rarely observed in the rectum. Appendiceal GISTs have similar features with small intestinal tumors by the common content of skeinoid fibers.

Esophagus

Leiomyomas are the most common esophageal mesenchymal neoplasms but rare in other regions of GI tract. Leiomyosarcomas are large, high-grade, and lethal tumors. GISTs are rare.

Omentum and mesentery

Omental GISTs can have spindle cell and epithelioid features resembling those of gastric GISTs, whereas mesenteric GISTs often have features resembling the small intestinal tumors including the presence of skeinoid fibers. These findings raise the possibility that omental and mesenteric GISTs are derived from the stomach and small intestine, respectively, representing tumors that for some reason have detached from their GI origin during their development.

Immunohistochemistry

Immunopheno typing is very important in the pathology laboratory for identification and differentiation of cell types. The presence of CD117 (c-Kit) on GISTs as revealed by immunohistochemical staining has now become one of the defining characteristics of this tumor and is an important confirmatory factor along with standard pathological evaluation. Furthermore, with the advent of targeted molecular therapy, the phenotype of GIST has added therapeutic relevance.

CD117

The CD117 antigen is an epitope in the extracellular domain of the surface tyrosine kinase receptor (c-Kit) whose ligand is stem cell factor (SCF). Activation of c-Kit by SCF causes dimerisation of the receptor, phosphorylation, and initiation of an intracellular signal transduction pathway that leads to regulation of cellular processes, including proliferation and differentiation. Although c-Kit is expressed on several cell types, including GIST, ICCs, mast cells, melanocytes, hematopoietic progenitor cells, and germ cells (Table 3)[16]. It is rarely (and not as abundantly) expressed on other spindle-cell tumors of the gut, such as smooth-muscle tumors and schwannomas, and thus can be used for differential diagnosis (Table 4)[16].

Hornick studied 365 soft tissue sarcomas and found the selectivity of c-Kit expression[21]. Most tumors were c-Kit negative; those that showed occasional focal staining of CD117 included Ewing sarcoma, melanoma, angiosarcoma, melanotic schwannoma, and extraskeletal myxoid chondrosarcoma. Chan also emphasized the presence of CD117 is not tumor specific (Table 5)[16].

CD117 positivity in GISTs is typically strong and global, often apparently pancytoplasmic (Fig. 10). Membrane staining is best observed in epithelioid GISTs, especially in dyscohesive, hypercellular, and sarcomatous variants. Some GISTs may have Kit positive and negative areas or perinuclear Kit-positive dots (golgi pattern). In some small intestinal GISTs, the areas rich in cell processes show greater Kit positivity than the cell bodies[19,22]. The best Kit antibodies currently available for formalin-fixed and paraffin-embedded tissue are polyclonal ones, whereas most

Table 3. Normal tissues expressing CD117/c-kit

Gastrointestinal tract	Sites outside gastrointestinal tract
interstitial cells of Cajal	A subset of CD34 positive haemopoietic stem cells
Mast cells	Melanocytes
	Basal cells epidermis
	Immature Langerhans cells in the epidermis
	Variety of epithelial cells (breast/salivary gland/sweat gland/renal tubule)
	Cells present in the reproductive system
	A subset of glial cells
	Osteoclast precursor

Table 4. Differential diagnosis of GISTs

Tumor	Histology	CD117	CD34	SMA	Desmin	S100	Cytogenetics and molecular genetics
GISTs	Spindle cell or epithelioid; fibrillary/ syncytial cytoplasm; most are monomorphic	+ (95% or almost 100%)	+ (60%-70%)	+ (30%-40%)	Rare (2%)	+ (5%)	Monosomies 14 and 22; Deletion of 1p; KIT mutations in up to 90%
Smooth muscle tumor	Most are spindle cell; variable atypia; well-formed fascicles; brightly eosinophilic cytoplasm	-	+ (10%-15%)	+	+	rare	Variable karyotype; no consistent pattern of gene involvement
Schwannoma	Spindle cell; short intersecting fascicles; lymphocytic infiltrate; variable palisading	-	+	-	-	+	Deletion of 22q; NF2 inactivation in about 50%

Table 5. CD117/c-kit positive tumors

Gastrointestinal tumors
  Gastrointestinal stromal tumors
Tumors occurring primarily outside the gastrointestinal tract
  Melanoma (loss in vertical growth phase and metastases)
  Clear cell sarcoma of tendons and aponeuroses
  Endometrial carcinoma
  Anaplastic small cell carcinoma of the lung
  Ewing's sarcoma group
  Anaplastic largecell lymphoma
  Reed-Sternberg cell in Hodgekin's lymphoma
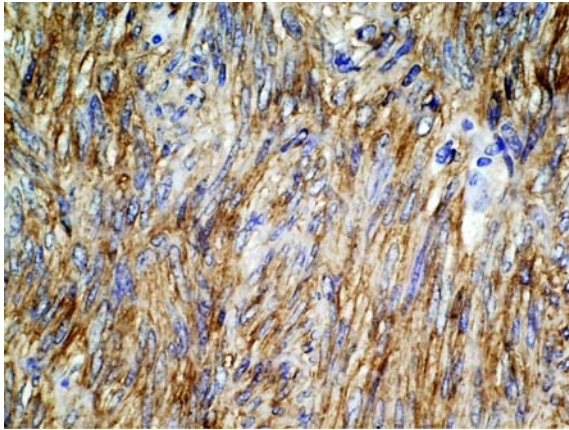 Mastocytosis
  Acute myeloid leukemia
  GliomaGerminoma

Fig. 10 Diffusely pancytoplasmic pattern of CD117 positivity (x400)

monoclonal Kit antibodies react inconsistently with GISTs. CD117 staining in frozen sections can be used if results are required more rapidly. The proportion of CD117 positive cells in GISTs is usually at least 90%, but may be as low as 5-20% in occasional tumors. This may account for the rare CD117 negativity in small biopsies of tumors with the morphology of a GIST. Some pathologists designate the tumors that have morphology of a GIST without expression of CD117 as GIST-like tumors. Mast cells and ICC in normal bowel wall are useful internal positive controls to supplement the normal positive and negative controls[22]. In Thailand, the previous diagnosis of the majority of other mesenchymal tumors of gastrointestinal tract has been changed to GISTs. This was supported with the increased incidence from 22% to 65% after the CD117 staining[23].

Approximately 5% of histologically suspected GIST are CD117 negative, and should be considered for molecular analysis for KIT or platelet-derived growth factor receptor alpha (PDGFRA) mutations[18]. Data on PDGRFA expression are scant, and many available antibodies are not reliable on paraffin-embedded tissue. However, some studies suggest that PDGFRA can be a diagnostic immunohistochemical marker[19].

CD34[12,19]

It is an antigen (transmembrane protein of unknown function) found most often on hematopoietic precursor cells, vascular endothelial cells, subsets of fibroblasts, and many neoplasms related to these cell types. It is also present on GIST cells, but to a lesser extent than CD117 (Table 6)[16]. The location of the primary GIST may be reflected in the percent positivity for CD34 (95-100% of esophageal and rectal GISTs, 80-85% of gastric GISTs, 50% of small intestinal GISTs). The malignant GISTs may show a slightly lower frequency of CD34 expression than the benign ones. CD34 expression has not been a significant prognostic factor in gastric and small intestinal GISTs.

DOG1[19,24]

A new gene identified in the vast majority of both KIT- and PDGFRA-mutated GISTs (GISTs independent of mutation type). This gene encodes for a protein of unknown function. It is absent in non-GISTs. Experience is limited and antibodies are not yet generally available. West described it as a cell membrane-associated protein, with markedly elevated expression in GISTs, DOG1 may also be a potential therapeutic target.

Muscle cell markers[19]

Approximately 30-40% of GISTs (especially in small intestinal GISTs) are positive for smooth muscle actin (SMA). The positivity for SMA varies from focal to extensive and can be equally prominent as Kit positivity in these tumors. SMA positivity has

Table 6. Immunohistochemical positivity for CD34 and CD117 in GISTs

CD117	CD34	Reference
100% (78/78)	72% (56/78)	4
94% (46/49)	82% (42/49)	8
88% (28/32)	69% (22/32)	4
81% (69/85)	56% (48/85)	20

been a statistically significant favorable prognostic factor in gastric and small intestinal GISTs. Desmin (an intermediate filament protein found in muscle cells) is rare in GISTs of all sites. Esophageal and gastric GISTs are more common and very rare in intestinal GISTs. Desmin positivity is more common in gastric epithelioid GISTs and is usually focal. The expression of myoid antigens (smooth muscle myosin and heavy molecular-weight caldesmon) in GIST is common and may be a reflection of multipotentiality of the ancestral Cajal cells or their relation with smooth muscle precursor cells.

Neural markers[17,19]

S100 protein (a neural crest cell antigen) is rare to be expressed in GISTs but seems to be more common in small intestinal than in gastric GISTs. Half of the cases with S100 positivity are also desmin and/or SMA positivity. Expression of only S100 is rare, although small numbers of S100 positive cells, probably representing entrapped Schwann cells, are not unusual. S100 positivity seemed to be an adverse prognostic factor in gastric but not in small intestinal GISTs according to the small number of cases in some studies. Neuron-specific enolase (NSE) immuno-reactivity is commonly seen in GISTs, but this is a non-specific feature because true smooth muscle tumors also may be positive[12].

Other markers[19]

Vimentin expression seems to be consistently positive. Keratin18 can be positive and may be more common in malignant GISTs. Keratin8 has a lesser degree of positivity. Keratin7,13,14,17,19 and 20 are negative. Antibody cocktails such as AE1/AE3 have usually negative results.

It has been suggested that expression of several markers of a given lineage correlates with a more favorable prognosis[12].

Ultrastructural features[17]

The ultrastructural findings in GISTs are variable depending on differentiation pathway. Neural differentiation shows synapse-like structures with dense core neurosecretory granules, endocytoplasmic vesicles, interdigitating cytoplasmic processes without basement membranes, and interstitial skeinoid fibers. Myogenic differentiation shows scattered mitochondria and prominent Golgi apparatus, strands of rough endoplasmic reticulum, focal accumulation of intracytoplasmic micro (myo) filaments (Fig. 11) with
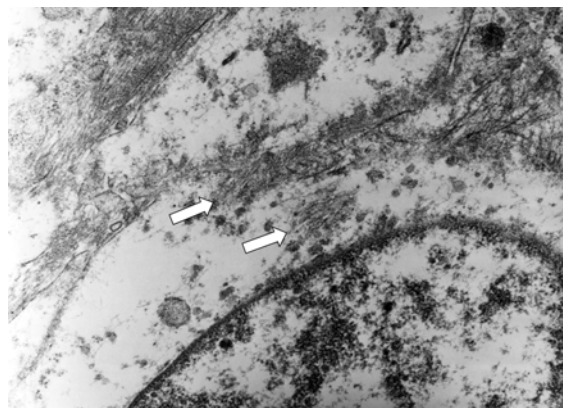

Fig. 11   The ultrastructure of GISTs shows intracytoplasmic myofilaments (arrow) (x40,000)

occasional focal condensations, subplasmalemmal attachment plaques and immature cell junctions, focal extracellular basal lamina material, and surface-oriented micropinocytotic activity.

The term GANT (gastrointestinal autonomic nerve tumor) was introduced by Walker and Dvorak, based on three cases that showed axonal-like differentiation with cell processes and small granular vesicles by electron microscopy[12]. GANTs are typically epithelioid or spindle cell neoplasms and usually of low histologic grade. They typically express S100, NSE, vimentin, and synaptophysin, and they are CD34 negative. GANTs can be distinguished from other GISTs only based on their unique ultrastructural features. Neural differentiation is required for its definitive diagnosis[17]. Tumors previously diagnosed as GANTs have subsequently been found to express KIT and have identical KIT mutations to GISTs. In addition, electron microscopy shows that a substantial proportion of GISTs have similar ultrastructural features to GANTs. Thus, GANTs should be regarded as a type of GIST and no longer be classed as a separate entity[1].

GIST pathogenesis: KIT and PDGFRA mutations

Kit is a transmembrane tyrosine kinase encoded by the KIT proto-oncogene located on chromosome 4q11-q12. It is nearly consistently expressed in all GISTs. The natural ligand of KIT is SCF (also known as the mast-cell growth factor, Steel factor, or the KIT ligand). Mutated KIT may not require SCF for dimerisation or autophosphorelation[1]. Most GISTs have activating mutations in the KIT receptor tyrosine

kinase and respond well to imatinib, which inhibits KIT kinase activity. KIT mutations have not been reported in true smooth muscle cell tumors. Thus, the presence of KIT mutations adds a further parameter that separates GISTs from true smooth muscle tumors[12]. Heinrich showed that 14/40 (35%) of GISTs lacking KIT mutations had activation mutations in the related receptor tyrosine kinase, PDGFRA[25]. KIT and PDGFRA genes encode for similarly named receptor tyrosine kinase proteins. PDGFRA gene is also located at 4q12. The corresponding proteins have structural characteristics of type III receptor tyrosine kinase family. Activation mutations of KIT and PDGFRA may lead to cellular proliferation and decrease in apoptosis. Mutations in KIT or PDGFRA receptor tyrosine kinase proteins observed in more than 80% of GISTs[19]. This may suggest that additional pathogenetic mechanisms exist in other cases, or that mutations occur in alternative sites[12].

Mutations within c-kit of the juxtamembrane domain, including deletions or point mutations in exon11 were described in GISTs. These mutations were shown to lead to spontaneous, ligand-independent tyrosine kinase activation. The mutations of c-kit in the exon 11 predominantly occur in those GISTs that are histologically and clinically malignant. Most of these mutations were in frame deletions of 3 to 18 base pairs, and a few were point mutations[12]. The other less common regions of mutations are in exon 9, exon 13, and exon 17. Most KIT-mutant proteins are sensitive to imatinib. However, exon 17 KIT-mutants in GIST are primarily resistant, and exon 9 KIT-mutants are less sensitive than exon 11 mutants. Exon 9 encoding the end of the extracellular domain is the second most often involved region of KIT. This mutation reported with a frequency of 5% to 13%. However, its apparent frequency depends on the ratio of intestinal to gastric tumors studied, because this mutation is nearly specific to intestinal GISTs. Missense mutations in exon 13 encoding the tyrosine kinase 1 domain have been reported with a low frequency (< 1%-2%). This mutation seems to be associated with malignant tumor behavior. It is sensitive to imatinib, which abolished the phosphorylated status of KIT in a cell line. Only a few GISTs with mutations involving exon 17 encoding the catalytic tyrosine kinase2 (phosphotransferase) domain of KIT have been reported[19].

PDGFRA has three different regions of mutation in GISTs. They are, in decreasing order of frequency, exon 18 (> 80% with missense mutation), exon 12, and exon 14. PDGFRA mutations show a strong predilection to gastric GISTs with epithelioid morphology. However, a few nongastric PDGFRA-mutant GISTs have also been reported, especially in the duodenum. The apparent frequency of these mutations depends on the ratio of gastric to intestinal and spindle to epithelioid GISTs studied. Exon 18 mutation is resistant to imatinib. Missense mutations of exon 14 seem to be associated with low KIT expression and unexpectedly favorable prognosis. Mutations of exon 12 are rare and most of them have missense mutations[19].

The technique for mutation screening may be performed on either formalin-fixed paraffin-embedded or frozen tumor samples, if a routine histological examination of the sample has been performed before nucleic acid extraction[18].

Prognostic factors: When GISTs are initially diagnosed, a minority (approximately 25% to 30%) are frankly malignant (metastasis or invasion of adjacent organs). The remains should be considered as having a potential for exhibiting malignant behavior and therefore are said to be of "uncertain malignant potential". GISTs are believed no truly benign tumors. The term "benign versus malignant" are being replaced with the more descriptive terms "low risk versus high risk" There is no established consensus on the predictability of malignancy in GISTs and no specific grading or staging system for GISTs. Grading system for other soft tissue sarcomas, is not relevant for GISTs, because specific modes of targeted treatments are used[19]. The several histological factors that have previously been associated with increased risk of malignancy include cellularity, necrosis, presence of cysts, atypical nuclei, tumor vascularity, histologic type, nuclear pleomorphism, size, and mitotic activity. The most consistent histopathologic features used to predict aggressiveness are tumor size and mitotic index[26]. Miettinen described that small tumors ($\leq$ 2 cm) and show mitotic activity not exceeding 5 mitoses per 50 high-power fields (HPF) have an excellent prognosis, probably independent of site, although this has not been shown specifically for all sites according to most of the data received from gastric and small intestinal tumors but less data on other rare sites. Tumors with a mitotic rate > 5/50 HPF usually have a malignant behavior[27]. Fletcher categorized GISTs into very low, low, intermediate, and high-risk tumors based on an estimation of their potential for recurrence and metastasis. Very-low-risk tumors measure $\leq$ 2 cm with mitotic activity < 5/50 HPF. Low-risk tumors measure between 2-5 cm with mitotic activity < 5/50 HPF.

Intermediate-risk tumors measure < 5 cm with mitotic activity 6-10/50 HPF or measure between 5-10 cm with mitotic activity < 5/50 HPF. High-risk tumors measure > 5 cm with mitotic activity > 5/50 HPF, tumors measure > 10 cm with any mitotic rate or any size tumors with mitotic activity > 10/50 HPF[26]. It has also been noted that anatomic location of the tumors may also be an important prognostic factor. For example, GISTs that arise in the small intestine may have a worse prognosis than those arising in the stomach[27].

Proliferation markers (Ki-67) may help identify tumors with malignant potential, but large site-specific series are not yet available and they have not been proven superior to mitotic counting[19]. High expression of Bcl-2, p53, vascular endothelial growth factor, and c-Myc proteins are frequently associated with poor prognosis[15]. The prognostic significance of KIT mutations is controversial. KIT mutations are not restricted to high-grade large tumors (poor prognosis) but are also observed in smaller, less mitotically active GISTs[15]. In conclusion, size and mitotic rate parameters are universally applicable. They probably should be recorded for all GISTs and included in the pathology report[19].

Treatment of GISTs: The standard treatment of localized resectable GISTs is surgery. The goal of surgery is complete resection of visible and micro-scopic disease. No consensus has concluded the need of preoperative diagnosis by core-needle biopsy (endoscopic or percutaneous). Intraabdominal open biopsy is also discouraged according to the risk of tumorspill because GISTs are very fragile and may bleed easily. GISTs are now considered as potentially malignant, they need to be resected, even small intra-mural lesions. However, since not all intramural lesions of the GI tract are GISTs, a preoperative pathological diagnosis should be obtained. GISTs tend to grow out of, not diffusely infiltrate, the primary organs, wedge resection of the stomach, segmental resection of the intestine, wide resection of the esophagus, duodenum, and rectum are considered an adequate treatment. Omental or mesenteric GISTs, a complete en bloc resections of visible disease is recommended. Adjacent organs adherent to the mass should be resected en bloc with the tumor, in order to avoid capsule rupture and intraabdominal spillage. Laparoscopic surgery should be avoided, owing to the higher risk of tumor rupture and subsequent peritoneal seeding[18].

GISTs that are inoperable (cannot be com-pletely resected or unresectable) and metastatic should be considered the medication with imatinib mesylate (Glivec, Novartis). It is a competitive inhibitor of all certain ABL tyrosine kinases, including: c-kit, c-ABL, bcr-ABL, and PDGFRA[11]. Imatinib mesylate inhibits these tyrosine kinases but has little or no effect on many other tyrosine or serine/threonine kinases. It competes with ATP for its kinase-binding site, and prevents the kinase from transferring phosphate from ATP to tyrosine residues of the substrates. This action inhibits downstream signaling from the kinase, which switches the balance towards apoptosis[1]. Radiotherapy and chemotherapy are not standard therapy. The role of radiotherapy is limited by the potential toxicity to surrounding structures, especially the intestines[22]. Attempts to treat malignant GISTs with systemic chemotherapy have been almost universally unsuccessful[1].

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Gastrointestinal stromal tumors (GISTs): ความสำคัญในทางพยาธิวิทยา

พัฒนา ศรมยุรา

Gastrointestinal stromal tumors (GISTs) เป็นเนื้องอกที่เกิดจากเนื้อเยื่อเกี่ยวพันที่พบได้บ่อยที่สุดของระบบ ทางเดินอาหาร เนื้องอกที่เกิดจากเนื้อเยื่อเกี่ยวพันนี้เดิมถูกเรียกว่า leiomyomas, schwannomas, leiomyoblastomas หรือ leiomyosarcomas ซึ่งในปัจจุบันได้ถูกจัดไว้ในกลุ่มของ GISTs โดยวิธีการศึกษาทาง histology immunohisto-chemistry และ molecular study เนื้องอกเหล่านี้มีต้นกำเนิดมาจาก stem cells ที่ต่อมาสามารถพัฒนาตัวเองไปเป็น เซลล์ที่กระตุ้นการบีบรัดตัวของกล้ามเนื้อผนังทางเดินอาหาร ตัวบ่งชี้การดำเนินโรค ที่สำคัญคือขนาดของเนื้องอก และ mitotic rate การผ่าตัดเป็นวิธีการรักษาหลักสำหรับเนื้องอกที่สามารถผ่าตัดได้ ส่วนเนื้องอกที่ได้แพร่กระจาย หรือไม่สามารถผ่าตัดได้ควรพิจารณาการรักษาด้วย tyrosine kinase inhibitor (imatinib mesylate) ซึ่งจะไปทำการ ยับยั้งที่ c-kit receptor ดังนี้จะเห็นได้ว่าในปัจจุบัน พยาธิแพทย์มีบทบาทในการวินิจฉัย GISTs การประเมินความเสี่ยง ของการที่จะเป็นเนื้องอกชนิดร้ายแรง การดำเนินโรค รวมทั้งการวางแผนในการรักษา อีกด้วย บทความนี้ได้ทบทวน รายงานทางการแพทย์อื่น ๆ ที่สำคัญเกี่ยวกับ GISTs และได้เน้นในส่วนที่เกี่ยวข้องกับงานของพยาธิแพทย์