Review article
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Gastrointestinal stromal tumors (GISTs): Definition, clinical, histological, immunohistochemical, and molecular genetic features, and predictors of malignant potential and differential diagnosis

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Gastrointestinal stromal tumors (GISTs) represent a distinct and the most important subset of mesenchymal tumors of the gastrointestinal (GI) tract. GISTs occur throughout the GI tract but are usually located in the stomach and small intestine. The cellular origin, differentiation, nomenclature, and prognosis of GISTs are controversial. Because GISTs, like the interstitial cells of Cajal, the GI pacemaker cells, express CD117 (c-kit protein), the origin of GISTs from the Cajal cells has recently been suggested. GISTs are also known for their wide variability in clinical behavior and for the difficulty to determine their malignant condition. The most reproducible predictors of malignancy are mitotic count >1-5 per10 high-powered fields (HPF), size >5 cm, tumor necrosis, infiltration and metastasis to other sites. However, some tumors with mitotic activity <1/10 HPF may metastasize indicating some uncertainty in malignant potential of GISTs, especially those larger than 5 cm. Recently, mutations in c-kit gene (exon 11) preferentially occur in malignant GISTs and may be a clinically useful adjunct marker in evaluation of GISTs. In conclusion, the strong CD117 expression mostly defines primary GI mesenchymal tumors as GIST. Specific identification of GIST may become clinically important if therapies targeting the c-kit tyrosine kinase activation become available.

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DEFINITION

Gastrointestinal stromal tumors (GISTs), previously classified as smooth muscle tumors, constitute the largest group of mesenchymal tumors of the gastrointestinal (GI) tract (1). These tumors encompass the majority of tumors earlier designated as leiomyomas, cellular leiomyomas, leiomyoblastomas and leiomyosarcomas of the GI tract, except in the esophagus, where typical leiomyomas are more common than GISTs (2-5).

They are defined as c-kit protein (CD117, stem cell factor receptor) - positive mesenchymal spindle cell or epithelioid neoplasms in the GI tract, omentum and mesentery (1,6).

The GISTs are often positive for CD34 (hematopioetic progenitor cell antigen), variably positive for smooth muscle actin (SMA), and usually positive for CD117. Many GISTs, especially the malignant ones, also have activating mutations in the exon 11 of the c-*kit* gene that are believed to be pathogenically important (3,7-9).

EPIDEMIOLOGY AND LOCALIZATION

GISTs account for approximately 1-2% of all GI tumors (1). They typically occur in older individuals, and the median age of patients with GIST of all locations varied in narrow range (59-64 years). The male/female ratio significantly differs from 1:1 among the patients with esophageal (4.3), rectal (2.8), colonic (1.9), and small intestinal GISTs (1.4-1.5) (1). The increasing number of these lesions seen in recent years is most likely due to advancement in diagnostic techniques.

These tumors may occur in any portion of the GI tract and may also

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be primary in the omentum and mesentery. They are most common in the stomach (60-70%), followed by small intestine (20-25%) colon and rectum (5%), and esophagus (<5%) (4, 5, 10).

GROSS PATHOLOGY AND CLINICAL FEATURES

GISTs may range in size from several millimeters to over 30 cm (11). In general, malignant tumors are larger that benign ones; however, size alone does not predict biologic behavior with certainty. Small GISTs appear as nodules, usually as an incidental finding during endoscopy or surgery. The larger tumors protrude intraluminally or to the serosal side. On section GISTs vary from slightly firm to soft, tan-white, often with foci of necrosis. Areas of hemorrhage may be prominent (Figure 1). Grossly, GISTs are tumors that appear within the muscularis propria of the GI tract; they may grow in an endophytic fashion (10, 12); other tumors may exhibit an endophytic or dumbbell growth pattern (12). Invasion of adjacent structures and organs, presence of multiple tumor nodules in the surrounding tissue, or obvious metastatic disease are characteristic of malignant GISTs.

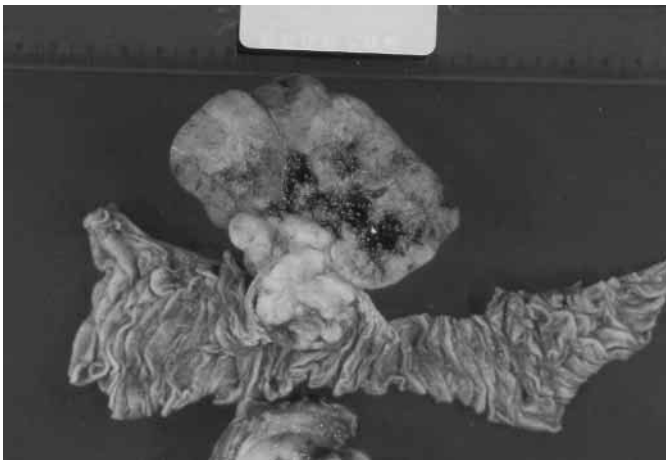

Figure 1. Cross-section of malignant small bowel GIST (9 cm diameter). Fleshy, tan-white tumor with foci of hemorrhages infiltrating the wall and surrounding tissue

The symptomatic lesions have manifestations that depend on tumor size, growth pattern, and location. The most common presenting symptoms are those of abdominal mass, frequently followed by GI bleeding (as a result of mucosal ulceration), and pain (10). The remainder of the symptom may include dysphagia, obstruction or perforation. Occasionally, duodenal GISTs may cause obstructive jaundice (12). Typical of the malignant GISTs is intra-abdominal spread and distant metastases most commonly to liver followed by lung and bone in decreasing frequency (13).

HISTOPATHOLOGY

Morphology: Cytologically, two basic cell types predominate: a spindled cell type and an epithelioid or round cell type. The spindled cell has an elongated nucleus with tapered, blunt, or rounded ends frequently with a clear perinuclear halo and moderately abundant pink cytoplasm. Spindled cells frequently exhibit an interlacing fascicular growth pattern. The epithelioid cell type has a polygonal or round contour with a central or slightly eccentric nucleus and moderately abundant cytoplasm. At times, the cytoplasm may appear densely eosinophilic exhibiting "rhabdoid" features. Epithelioid cells frequently exhibit a sheet-like growth pattern (12). Either cell type may have benign or malignant cytological features with nuclear pleomorphism, hyperchromasia, and prominent nucleoli. A variable intense mononuclear inflammatory cell infiltrate admixed with eosinophils may be present (12).
The majority of gastric GISTs are spindle cell tumors that show a variety of histological patterns. The epithelioid pattern occurs in approximately one-third of gastric GISTs and corresponds to tumor previously designated as leiomyoblastoma or epithelioid leiomyosarcoma (Figure 2).

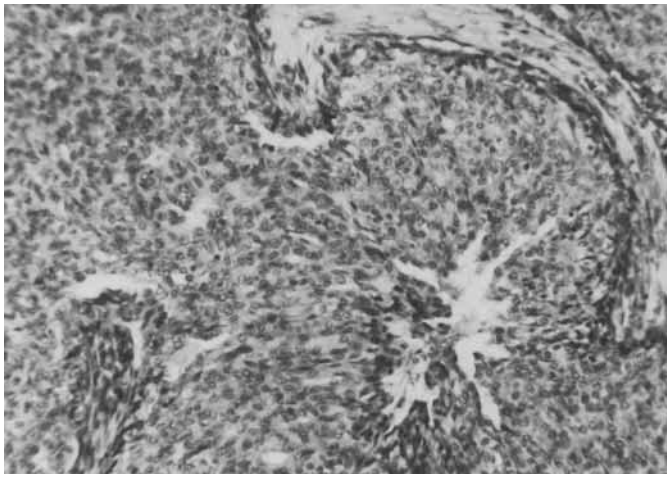

Figure 2. Malignant gastric GIST. Epithelioid cell type, zonal necrosis, and numerous mitotic figures (magnification x 400)

Small bowel GISTs histologically resemble to those of the stomach, although epithelioid lesions are uncommon. Globoid extracellular collagen accumulation (so-called skenoid fibers) is frequently observed, especially in benign tumor (14).
Immunohistochemistry: The origin and differentiation of GISTs have been a cause of a recent speculation and controversy. In the preimmunohistochemical era, location within muscularis propria of the bowel and frequent spindle cell morphology implied a smooth muscle origin. Early immunohistochemical reports yielded conflicting data, which suggest spectrum differentiation within GISTs. Recent studies show that most of GISTs are strongly reactive to the antibody CD117 (c-kit protein), a membrane receptor with an internal tyrosine kinase component (3, 7, 8, 15, 16). The c-kit positivity of GISTs matches the one seen in the interstitial cells of Cajal (ICCs), the pacemaker cells regulating autonomic activity (8,17). ICCs are found throughout the GI tract within myenteric plexus, submucosa and individually within muscularis propria. Based on this and the expression of an embryonic form of smooth muscle myosin heavy chain in GISTs and Cajal cells,

the origin from Cajal cells has been suggested (3, 8,18). However, considering the origin of Cajal cells and smooth muscle from a common precursor cell (19), the hybrid Cajal cell and muscle cell seen in many GISTs, their origin from a precursor cell pool with differentiation towards a Cajal cells phenotype is more likely (4). Electron microscopic observation showing hybrid nerve and smooth muscle features in many GISTs are also consistent to the origin from a multipotential precursor cell (4). Immunohistochemically, GISTs are positive for CD117. The positivity typically appear as diffuse cytoplasmic staining with common membrane accentuation, but in some cases, it is focally perinuclear "Golgi zone-like staining" (1, 4). The CD34 positivity (commonly a membrane pattern) varies from 47% in small bowel, and 96% to 100% in rectum and esophagus. Smooth muscle actin (SMA) expression shows the opposite pattern, which is the most frequent in the GISTs of small bowel (47%) and the rarest in the GISTs of rectum and esophagus (10-13%) (1). A few GISTs show reactivity for desmin (<5%) (1, 9), and very few for S100-protein, usually weak reactivity (9); however, S100 positivity is frequently seen in small intestine GISTs (15%) (1).

MOLECULAR GENETICS

Some GISTs, more commonly the malignant ones, show mutations in the regulatory juxtamembrane domain (exon 11) of the c-kit gene (9, 15). The c-*kit* gene encodes a type III receptor tyrosine kinase (20), which consists of an extracellular domain, a transmembrane domain, a juxtamembrane domain, and tyrosine kinase domain. The stem cell factor (SCF) is the ligand for the c-kit receptor. Mutations of the c-*kit* gene are found in multiple GISTs (9, 15). Families with germ line mutation of the c-*kit* gene, GISTs and cutaneous hyperpigmentation have also been described (21, 22). These c-*kit* mutations represent gain-of-function mutations leading to ligand-independent activation (autophosphorylation) of the tyrosine kinase and further the phosphorylation cascade that leads into mitotic activation (15, 21). The most common mutations appear to be in-frame deletion of 3-21 base pairs, followed by point mutations and occasionally described insertions (9, 15, 23).

Other genetic changes in GISTs discovered using genomic hybridization include losses in 14q and 22q in both benign and malignant GISTs. Losses in 1p and chromosome 15 are less frequent. Gains and high level amplifications occur in malignant GISTs in 3q, 8q, 5q and Xp (24).

PREDICTIVE FACTORS AND PROGNOSIS

The prognosis of GISTs largely depends on the mitotic count, size, depth of invasion, and presence or absence of metastases (13). Cellular pleomorphism and anatomic sites are not significant features (13). Tumors less than 5 cm are usually benign. Size, however, is not entirely a reliable predictor of biological behavior, because tumors <5 cm in size have been known to metastasize. The most reproducible and reliable predictor of malignant potential is mitotic count. In general, mitosis ranging from >1-5/10 high power fields (HPF) is associated with increased metastatic potential. GISTs can further be divided into low (<10 mitosis/10 HPF) and high-grade (>10 mitosis/10 HPF) lesions. Benign stromal tumors by default are those with 0-1 mitosis/10 HPF (12). It must be noted that although a high mitotic index signals malignancy, a low mitotic index (<1/10HPF) does not always guarantee a benign course of GISTs, especially those larger than 5 cm. Intratumoral necrosis is also indicative of poor prognosis. DNA-ploidy, high proliferative index (over >10%) by proliferation markers (especially Ki-67) may reflect higher malignant potential (25, 26). Recently, a senseless mutation in the c-*kit* gene (exon 11) has been found in those GISTs that exhibit malignant behavior (9, 23). The patients who display this mutation show more frequent recurrences and higher mortality than patients with mutation-negative GISTs. Accordingly, mutation in the c-*kit* gene is associated with poor prognosis in patients with GISTs (9, 23).

The clinical outcome of patients with GIST was recently highlighted in a report on 200 patients with GIST collected over a span of 16 years (27). Recurrence following a complete resection was common and involved both local (52%) and distant sites (67%). Fifty percent of all first-site recurrence involved the liver (27). The 5-year disease-specific survival for GIST was 28% (28). Radical resection yielded 5-year survival rates of 54% and 65% (27) .

DIFFERENTIAL DIAGNOSIS

GISTs differ from true leiomyosarcomas (rare in the GI tract) and leiomyomas clinically and pathogenically. Leiomyomas occur in the GI tract in two forms: esophageal mural leiomyomas, and leiomyomas involving the muscularis mucosae layer of the colorectum. Histologically, the tumors have on overall basophilic appearance and show combinations of solid, mixoid, and perivascular collarlike patterns with a spindle or epithelioid histology (5). GI leiomyomas are immunohistochemically distinctive from GISTs as CD117 negative tumor (5). They are typically positive for smooth muscle actin (SMA) and desmin (1). Leiomyosarcomas show evident smooth muscle differentiation histologically and immunohistochemically. They are mitotically active tumors composed of spindled, well-differentiated smooth muscle cells with blunt-ended nuclei and variably eosinophilic cytoplasm showing significant nuclear atypia (10). Leiomyosarcomas are positive for SMA and desmin, and are negative for CD34, CD117 and S-100 protein (1). In contrast to the behavior of GISTs, leiomyosarcomas have a different pattern of metastases, involving pulmonary sites while less commonly

spreading to the liver (28).

GISTs also differ from schwannomas that are benign S-100 positive cell tumors generally presenting in the stomach (1). Histologically, GI schwannomas usually show a spindle cell pattern like cellular schwannoma with vague nuclear palisading. The tumors often have sprinkled lymphocytes and nodular lymphoid cuff. The distinction between schwannoma and GIST is important because the former is benign even when it is large and mitotically active.

Other mesenchymal tumors that have to be separated from GISTs include inflammatory fibroid polyps, and inflammatory myofibroblastic tumors in children. Inflammatory fibroid polyps of the GI tract are negative for CD117 (1), but are often positive for CD34 (1, 29). Inflammatory myofibroblastic tumors in children are negative for CD117 and CD34, but some show CD117 positive endothelia (1, 30).

Gastrointestinal autonomic nerve tumor (GANT) (Figure 3) or previous designation plexosarcoma, shows ultrastructural features of autonomic neurons: cell processes with neurosecretory type dense core granules and arrays of microtubules (31). Histologically, such tumors show a variety of spindle cell and epithelioid patterns similar to those seen in GIST; at least some of these tumors are positive for CD117. GANTs are probably a subset of GISTs.

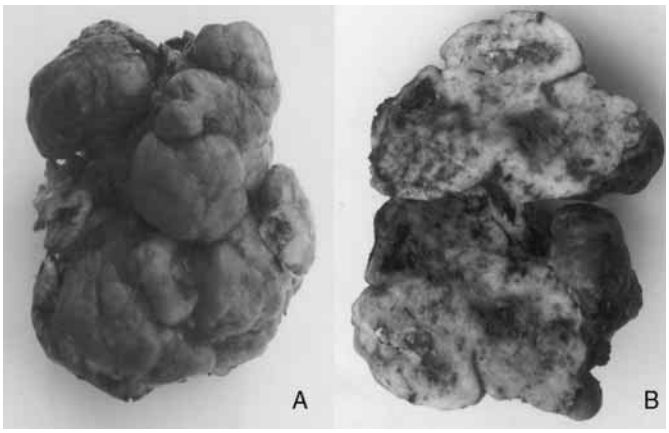

Figure 3. GANT of the stomach. A. Multilobular macro aspect. B. Cut surface

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