Virchows Arch (2001) 438:1–12
DOI 10.1007/s004280000338

REVIEW ARTICLE

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Gastrointestinal stromal tumors – definition, clinical, histological, immunohistochemical, and molecular genetic features and differential diagnosis

Received: 6 July 2000 / Accepted: 26 September 2000 / Published online: 14 December 2000

Abstract Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal tumors of the gastrointestinal (GI) tract. They are defined here as KIT (CD117, stem cell factor receptor)-positive mesenchymal spindle cell or epithelioid neoplasms primary in the GI tract, omentum, and mesentery. GISTs typically present in older individuals and are most common in the stomach (60–70%), followed by small intestine (20–25%), colon and rectum (5%), and esophagus (<5%). Benign tumors outnumber the malignant ones by a wide margin. Approximately 70% of GISTs are positive for CD34, 20–30% are positive for smooth muscle actin (SMA), 10% are positive for S100 protein and <5% are positive for desmin. The expression of CD34 and SMA is often reciprocal. GISTs commonly have activating mutations in exon 11 (or rarely exon 9 and exon 13) of the KIT gene that encodes a tyrosine kinase receptor for the growth factor named stem cell factor or mast cell growth factor. Ligand-independent activation of KIT appears to be a strong candidate for molecular pathogenesis of GISTs, and it may be a target for future treatment for such tumors. Other genetic changes in GISTs discovered using comparative genomic hybridization include losses in 14q and 22q in both benign and malignant GISTs and occurrence in various gains predominantly in malignant GISTs. GISTs have phenotypic similarities with the interstitial cells of Cajal and, therefore, a histogenetic origin from these cells has been suggested. An alternative possibility, origin of pluripotential stem cells, is also possible; this is supported by the same origin of Cajal cells and smooth muscle and by the common SMA expression in GISTs. GISTs differ clinically and pathogenetically from true leiomyosarcomas (very rare in the GI tract) and leiomyomas. The latter occur in the GI tract, predominantly in the esophagus (intramural tumors) and the colon and rectum (muscularis mucosae tumors). They also differ from schwannomas that are benign S100-positive spindle cell tumors usually presenting in the stomach. GI autonomic nerve tumors (GANTs) are probably a subset of GIST. Other mesenchymal tumors that have to be separated from GISTs include inflammatory myofibroblastic tumors in children, desmoid, and dedifferentiated liposarcoma. Angiosarcomas and metastatic melanomas, both of which are often KIT-positive, should not be confused with GISTs.

Keywords Gastrointestinal stromal tumors · Smooth muscle actin · GI tract · GI autonomic nerve tumors

Introduction

Gastrointestinal stromal tumors (GISTs) are specific mesenchymal tumors of the GI tract that may occur in the entire length of the GI tract, from the esophagus to the anus and, sometimes, even in the omentum and mesentery adjacent to but separate from the stomach and intestines. These tumors have a wide clinical spectrum from benign, small, incidentally detected nodules to frankly malignant tumors. The recent understanding on their molecular pathogenesis, namely common presence of activating mutations in the gene encoding KIT, may have significant clinical importance, making it necessary to accurately define and clinically diagnose these tumors and separate them from other mesenchymal tumors of the abdomen.

In the earlier literature, GISTs were designated as smooth muscle tumors: leiomyomas, cellular leiomyomas, leiomyoblastomas, and leiomyosarcomas [2]. However, electron microscopic studies in the 1960s demonstrated a lack of typical smooth muscle differentiation in

The opinions and assertions contained herein are the expressed views of the authors and are not to be construed as official or reflecting the views of the Departments of the Army or Defense. Supported by American Registry of Pathology.

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gastric leiomyoma [78]. Mazur and Clark [35] found that the GI mesenchymal tumors of the stomach, formerly defined as leiomyomas, lacked immunohistochemical features of Schwann cells (S100 protein negative) and did not have ultrasturctural characteristics of smooth muscle cells. Therefore, these authors used the histogenetically neutral designation "gastric stromal tumors", which subsequently has become applied to other, similar tumors in the intestines, and GIST has become the widely applied term now used on the specific mesenchymal tumors of the GI tract.

Because the majority of all mesenchymal tumors of the GI tract (except esophagus) are GISTs, older data on gastric and intestinal smooth muscle tumors [1, 17, 53, 67] largely reflect GISTs. This review will discuss the definition, clinical behavior and prognostic factors, and histological and immunohistochemical spectrum of GIST, pathogenesis and genetics, and the relationship between GISTs and smooth muscle tumors and GISTs and GANTs. The differential diagnosis of GISTs from other mesenchymal tumors of the GI tract will also be discussed.

Definition of gastrointestinal stromal tumors

Gastrointestinal stromal tumors (GISTs) are defined here as cellular spindle cell, epithelioid, or occasionally pleomorphic mesenchymal tumors of the gastrointestinal (GI) tract that express the KIT (CD117, stem cell factor receptor) protein, as detected using immunohistochemistry. The majority of GI mesenchymal tumors are GISTs and are strongly and nearly uniformly KIT positive. Relatively few other tumors may also be KIT positive, but these tumors, metastatic melanoma, angiosarcoma, pulmonary small cell carcinoma, Ewing sarcoma, some other carcinomas, mastocytoma, and seminoma, only rarely enter in the differential diagnosis of GISTs [3, 42, 44, 48, 72].

This definition specifically excludes gastrointestinal true smooth muscle tumors (leiomyomas and leiomyosarcomas) and schwannomas and neurofibromas. There is a small, somewhat problematic group of tumors that are in the histological range but do not express KIT. These undifferentiated mesenchymal tumors typically lack all other cell-type markers employed in the differential diagnosis of GIST [CD34, smooth muscle actin (SMA), desmin and S100-protein]. The classification of such tumors with a "null-phenotype" is open. Some investigators may include them among GISTs (when applied in a broad sense), whereas others may exclude them. Correlated morphologic and molecular genetic studies are necessary to determine whether or not these tumors biologically belong to the GIST group.

Epidemiology

According to a population-based sample, we estimate the incidence of GISTs as 10–20/million. Of these, 20–30% are malignant tumors. GISTs typically occur in older individuals over 50 years of age [40]. The median ages in the largest series of GISTs of different locations have ranged between 55 years and 65 years. Some series show a male predominance, and others show equal gender distribution [32, 40, 43, 75]. GISTs are rare before the age of 40 years, and they are very rare in children; we have found that many tumors earlier classified as gastrointestinal smooth muscle tumors in children actually are inflammatory myofibroblastic tumors.

GISTs are most common in the stomach (60–70%), followed by small intestine (20–30%), colon and rectum (5%), and esophagus (<5%). Occasional GISTs primary in the omentum and mesentery have also been reported [38]. The primary site for a malignant GIST extensively involving the abdominal cavity may be impossible to determine.

Clinical presentation

Small GISTs are often incidentally detected on gastric or small intestinal serosa during surgery for other conditions, for example, during gall bladder or gynecologic surgery. GISTs may also be detected during a gastroscopy as submucous nodules or occasionally as incidental radiologic findings. For example, some esophageal GISTs analyzed by us were seen as esophageal masses in routine chest X-ray [41]. Small rectal GISTs may be palpated during routine physical examination (in men during prostate cancer screening and in women during gynecologic examination).

The symptomatic GISTs of the esophagus typically present with dysphagia or occasionally as a mediastinal tumor that at surgery is found to be connected with the esophagus [41]. Gastric and small intestinal GISTs often present with vague symptoms leading to their gastroscopic or radiologic detection, but sometimes they cause upper gastrointestinal bleeding [53, 67, 75]. Colorectal GISTs may manifest with lower GI bleeding, colonic perforation, pain, obstruction, or combination thereof [43]. A minority of GISTs, usually malignant tumors, may be externally palpable.

Tumor behavior and prognostic factors

Study of larger series of GISTs, defined as KIT-positive tumors, reveals that these tumors have a spectrum of clinical behavior at all sites of their occurrence. In the stomach, the most common site of GIST benign tumors outnumber the malignant ones by a wide margin (3–5:1), whereas most esophageal and colonic GISTs are malignant.

The incidental small GISTs have an invariably benign clinical behavior, probably contributed by the fact that their complete excision is easy. Tumors that show low mitotic frequency (five or fewer mitoses per 50 HPF) usually have a benign behavior. However, there is a defi-

nite percentage of mitotically inactive tumors that subsequently metastasize, emphasizing the fact that low mitotic count does not rule out a malignant behavior [19, 53]. Therefore, the designation "uncertain malignant potential" applies to a significant number of GISTs; at least a close follow-up is needed in such cases. Since the GISTs with low mitotic count and malignant behavior are usually larger tumors, a combination of low mitotic rate and small size (smaller than 5 cm) may more accurately predict a benign behavior. However, gastric tumors seem to behave less aggressively than small intestinal tumors of similar size and mitotic activity [14, 75].

GISTs with mitotic counts over five per 50 HPF are customarily designated as malignant, and tumors over 50 mitoses per 50 HPF are designated as high-grade malignant. Such tumors have a high risk for diffuse intra-abdominal spread and liver metastasis, the two principal ways of the spread of malignant GISTs [19]. Bone and lung metastases are rare [17, 67]. Soft tissue metastases may be seen in the internal aspect of the abdominal wall and occasionally in the subcutis.

The clinicopathologic adverse prognostic factors tested in large series of GISTs and found significant in at least one investigation include aneuploidy on DNA flow cytometry [6, 7, 27, 55], tumor size less than 5–6 cm [6, 7, 55], presence of coagulative tumor necrosis [32], and high Ki67-analog score [13, 55]. The presence of peritoneal seeding at the primary operation is an adverse prognostic sign [6, 7, 32].

Histological spectrum of GISTs at different sites

The range of histological appearances of GISTs at different sites has been illustrated in Fig. 1. All tumors shown in these figures have been documented as KIT-positive primary gastrointestinal neoplasms. The most common histological variants among the gastric GISTs include cellular spindle cell tumors with moderate to slight interstitial collagen. Some of these tumors have a prominent, nerve sheath tumor-like nuclear palisading pattern, while others show prominent perinuclear vacuolization. GISTs with epithelioid appearances correspond with the previous designation of leiomyoblastoma and may have either solid or myxoid pattern, and occasionally show a paraganglioma or carcinoid-like compartmental pattern. Small intestinal GISTs often contain extracellular collagen globules (skeinoid fibers), as originally ultrastructurally and histologically described by Min [46]. GISTs of the colon and rectum are almost always spindle cell tumors, and the rectal GISTs often have a bland histology. Malignant GISTs may have a spindled, round cell, or epithelioid pattern and combinations thereof; the malignant GISTs are not as easy to fit into cell-type classification as the benign ones. Some malignant GISTs histologically resemble leiomyosarcomas, although they usually have a less eosinophilic cytoplasm. Significant nuclear pleomorphism is rare.

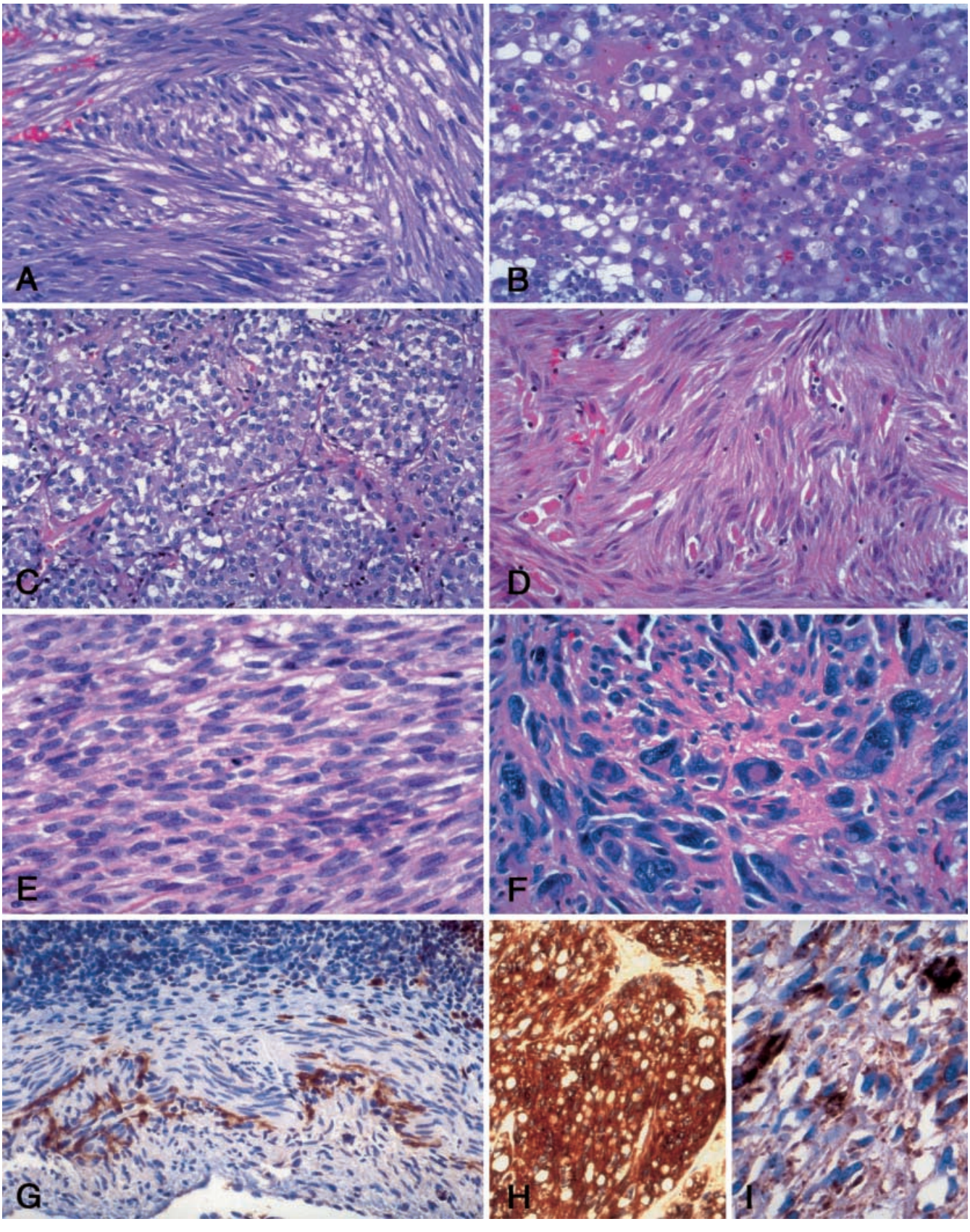
KIT protein in GISTs and its histogenetic significance

GISTs are defined here as immunohistochemically KIT-positive tumors. Typically, such positivity is widespread in the entire tumor and appears as strong, cytoplasmic staining, sometimes with membrane and golgi-zone accentuation (Fig. 1). [24, 44, 61, 68]. According to our experience, KIT positivity is often weaker in the epithelioid GISTs. The KIT protein (CD117 in the standardized terminology of leukocyte antigens) is a transmembrane growth factor receptor for stem cell factor (SCF) and, therefore, also termed as SCF receptor. The KIT protein belongs to the family of receptor tyrosine kinases and is structurally and functionally closely related to macrophage colony stimulating factor receptor. The KIT receptor normally becomes dimerized and its tyrosine kinase phosphorylated (activated) upon the ligand binding, then enabling it to phosphorylate other proteins in the signal transduction pathway that ultimately carry the proliferation signal into the nucleus [26].

KIT-positive normal cells in the gastrointestinal tract are the interstitial cells of Cajal, autonomic nerve related gastrointestinal pacemaker cells that regulate the intestinal motility [34, 59]. Their functional significance became apparent based on experiments where mice with defective KIT protein had disturbance of intestinal motility and died of paralytic ileus [34]. Cajal cells can be seen in the adult intestine in and around the myenteric plexus and in fetal intestine as an extensive belt-like formation in the outer smooth muscle layer (Fig. 1). Because the immunohistochemical and ultrastructural similarities between Cajal cells and GISTs, an histogenetic origin of GISTs of Cajal cells was proposed [24, 68]. Recently, such a theory was supported by the shared embryonic myosin expression in Cajal cells and GISTs as reported by Sakurai et al. [56]. The origin of GIST from CD34-positive subset of Cajal cells was also suggested based on coexpression of KIT and CD34 and their transcript in a subset of explanted murine Cajal cells [54].

Another possibility is that GISTs originate from the primitive stem cells that can differentiate into both Cajal cells and smooth muscle cells. Chimeric development experiments on birds and mice have shown that the Cajal cells and smooth muscle originate from a common precursor [31, 81]. The capability of Cajal cells to differentiate into smooth muscle cells following the blockade of the KIT signaling pathway suggests that they may have multipotential stem cell-like capabilities [71]. If subsets of Cajal cells represent such common precursor cells, this would reconcile the theories on GIST origin from Cajal cells versus stem cells.

KIT is also constitutively expressed in mast cells, which serve as an excellent internal control in immunohistochemistry. This receptor is also present in hematopoietic stem cells, melanocytes, germ cells, certain cutaneous basal, and skin adnexal and mammary ductal epithelia [3, 26, 72]. The functional significance of KIT in some of these cell types has been demonstrated experi-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mentally. For example, the KIT-deficient mice developed anemia and loss of pigment and reproductive function [26]. Among human tumors, KIT is usually found in mast cell neoplasia [3], over 50% of angiosarcomas [42], melanomas, although often with reduced expression in metastasis [48, 72], and in seminoma/dysgerminoma [72]. Other mesenchymal tumors, most notably typical leiomyosarcomas and liposarcomas, may contain isolated KIT-positive cells [44]. However, considering that all GISTs are typically globally KIT positive, the other sarcomas with sporadic KIT-positive cells are not likely to be confused with GISTs.

Other cell-type markers in GISTs

Approximately 60–70% of all GISTs are positive for CD34, the hematopietic progenitor cell antigen also expressed in endothelial cells and subsets of fibroblasts and their tumors [37, 44, 45, 47, 69, 73]. Based on analysis of nearly 300 GISTs, the esophageal and rectal GISTs have the highest frequency of CD34 positivity (over 90%). There seems to be no significant difference in the expression of CD34 in benign versus malignant gastric GISTs (85%). The small intestinal GISTs show the lowest percentage of CD34 positivity, 50% among both benign and malignant tumors [44].

A significant subset of GISTs (that are defined as KIT-positive tumors) also express SMA, typically present in normal and neoplastic smooth muscle cells and some myofibroblasts [18, 44]. Such expression may be focal or global and, interestingly, is reciprocal with CD34 expression: the SMA-positive tumors are often CD34 negative and vice versa. Also, some tumors show a “mosaic-pattern” with actin-positive and CD34-negative areas and vice versa [44]. In some cases, the SMA positivity of the entrapped smooth muscle fibers may be difficult to separate from the reactivity of the GIST cells.

Desmin, the intermediate filament protein of 53 kDa typical of smooth, skeletal and cardiac muscle cells, is only rarely expressed in GISTs. If present, it is almost always limited to scattered tumor cells. We have found that approximately 5–10% of GISTs contain desmin-positive tumor cells [44]. Such positivity may be more common among the epithelioid GISTs. Although GISTs are typically S100 negative, a definite percentage of them, approximately 10% of GISTs, have cytoplasmic and nuclear S100 protein positivity. The combination of KIT and S100 protein positivity separates GISTs immunohistochemically from gastrointestinal Schwann cell tumors [44].

Heavy caldesmon (HCD), an actin binding, cytoskeleton-associated protein, is typically expressed in GISTs, similar to true smooth muscle tumors (leiomyomas and leiomyosarcomas) [39] (Fig. 1). Similar to SMA, HCD is also present in myoepithelial cells. Its presence in GISTs is compatible with a cell type that is related to or can differentiate toward smooth muscle cells. As mesenchymal tumors, GISTs are typically strongly positive for vimentin. They are negative for neurofilaments and glial fibrillary acidic protein. In our experience, expression of simple epithelial keratins is much rarer than that observed in typical leiomyosarcomas and occurs especially in malignant epithelioid GISTs.

KIT gene mutations in GISTs

Hirota et al. first described activating mutations in exon 11 of the c-kit gene, which is an internal, juxtamembrane domain with a regulatory function. They were shown to lead to ligand-independent phosphorylation (activation) of the KIT tyrosine kinase, and the stable transfection of murine lymphoblast cell line with the mutant c-kit had a transforming effect in vitro [23]. Familial GISTs were also reported in patients with an activating germline KIT mutation [51]. Kitamura et al. comprehensively discussed the biology of the c-kit gene and its mutations in a recent review [26]. It is believed that activation of KIT, independent of the growth factor signal, has a central pathogenetic importance.

Subsequent studies have confirmed the presence of mutated KIT in approximately half of GISTs [16, 28, 70]. However, others have reported lower frequencies (15–31%) of similar KIT mutations in GISTs [49, 57]. No mutations were found in esophageal leiomyomas or prototypic leiomyosarcomas, suggesting different pathogenesis for these tumors [28]. KIT mutations occur predominantly in malignant GISTs [16, 28, 70] and were suggested as an independent prognostic marker [70]. These mutations were most frequently found in the proximal part of exon 11 at codons 550–562 and represented in frame deletions or missense point mutations. Also, an activating mutation in the distal part of exon 11 (deletion of codon 579) was documented [50]. Occasionally, duplication of one to several codons are seen in the distal part of exon 11 [49] (Lasota, unpublished observations), but biological importance of these types of mutations have not been confirmed.

Since half of the GISTs lack mutations in the juxtamembrane domain, the possibility was evaluated that activating KIT mutations might occur in other KIT domains. Taniguchi et al. [70] did not find mutations in the tyrosine kinase domain (exon 17) in 124 GISTs. Codon 816 of the KIT tyrosine kinase domain is typically mutated in mastocytoma [70].

Recently, Lux et al. [33] sequenced KIT transcripts from GISTs and found mutations in the extracellular do-

◀ **Fig. 1** Examples of the histological patterns of gastrointestinal stromal tumors (GISTs), Cajal cells, and GIST immunohistochemistry. **A** Gastric spindle cell GIST. **B** Gastric epithelioid GIST. **C** Gastric epithelioid GIST with carcinoid-like compartmental pattern. **D** Spindle cell small intestinal GIST with skeinoid fibers. **E** Malignant gastric GIST with resemblance to leiomyosarcoma. **F** Malignant gastric GIST with pleomorphism. **G** KIT (CD117)-positive interstitial cells of Cajal around the myenteric plexus between the circular and longitudinal muscle cell layers of fetal small intestine. **H** KIT-positive GIST with prominent perinuclear vacuoles. **I** Heavy caldesmon-positive GIST

main (exon 9) and the kinase domain (exon 13) of KIT. These mutations were duplications of six nucleotides, encoding Ala^{502}-Tyr^{503} in exon 9 and a missense mutation, resulting in substitution of Glu for Lys^{642} in exon 13. The homozygous exon 13 mutations were associated with constitutive KIT tyrosine phosphorylation. Mutations in exon 9 and exon 13 were found in 8 of 12 GISTs (61%) that were negative for exon 11 mutations, and authors concluded that these mutations cover a substantial balance of those GISTs that lack exon 11 mutations. Our experience, based on a study of 200 GISTs, confirms the occurrence of mutations in these two new "hotspots" in exon 9 and exon 13. However, these mutations are rare events and cover only a minority (less than 10%) of those GISTs that do not have exon 11 mutations [29]. Figure 2 shows examples of sequences of the mutated KIT gene in GISTs. Figure 3 shows the predicted amino acid sequences of the different types of KIT mutations.

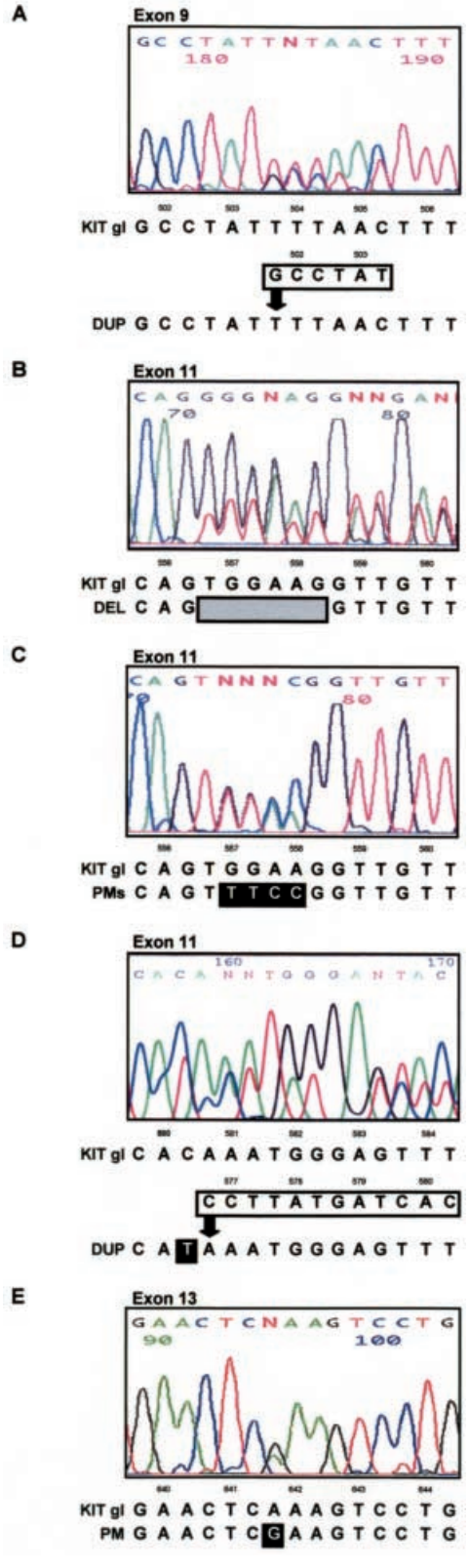

Fig. 2 Examples of direct sequencing of KIT (CD117, stem cell factor receptor) exons 9, 11, and 13 in five gastrointestinal stromal tumors (GISTs). **A** Duplication of codons 502 and 503 in exon 9. **B** Deletion of codons 557 and 558 in exon 11. **C** Four point mutations clustered in codons 557 and 558. **D** Duplication of codons 577–580 in exon 11. **E** Point mutation in codon 642 in exon 13. The *gray box* indicates a deletion, and point mutations are marked by *black squares*. Inserted sequences are shown in *clear boxes*. *Arrows* indicate the points of insertion. The codon numbers are indicated above the sequences. *DUP* duplication; *DEL* deletion; *PM* point mutation; *c-kit gl* c-kit germline

Potential therapeutic interventions to KIT activation

The activating mutations in the c-kit gene in GIST are potential targets for therapeutic intervention of GISTs. Therapeutic trials may examine the potential of countering the pathologic activation of KIT tyrosine kinase, as is being explored with other tumors with tyrosine kinase signal transduction activation [66, 79]. The potential for a specific treatment targeting the molecular pathogenesis of GIST makes it important to specifically recognize these tumors and separate them from other mesenchymal tumors that have a different molecular pathologic pathway. The separation of GISTs from other mesenchymal tumors is also important for the evaluation of the response of these tumors to conventional therapies.

Other genetic changes in GISTs

Cytogenetic data on gastrointestinal leiomyosarcomas probably largely apply to GISTs. In a review on cytogenetics of soft tissue tumors, Sandberg and Bridge summarized the data on leiomyosarcomas. Among them were those of gastrointestinal origin [58]. These tumors often showed complex karyotypes, including common losses of chromosomes 14 and 22 [9].

Some of these changes have been confirmed using comparative genomic hybridization (CGH) [10, 62]. This method can be used to globally survey the DNA copy number changes in each chromosomal band in the tumor compared with normal cells. Such studies can pinpoint the areas of losses that may contain tumor suppressor genes. The areas that contain gains or high level amplifi-

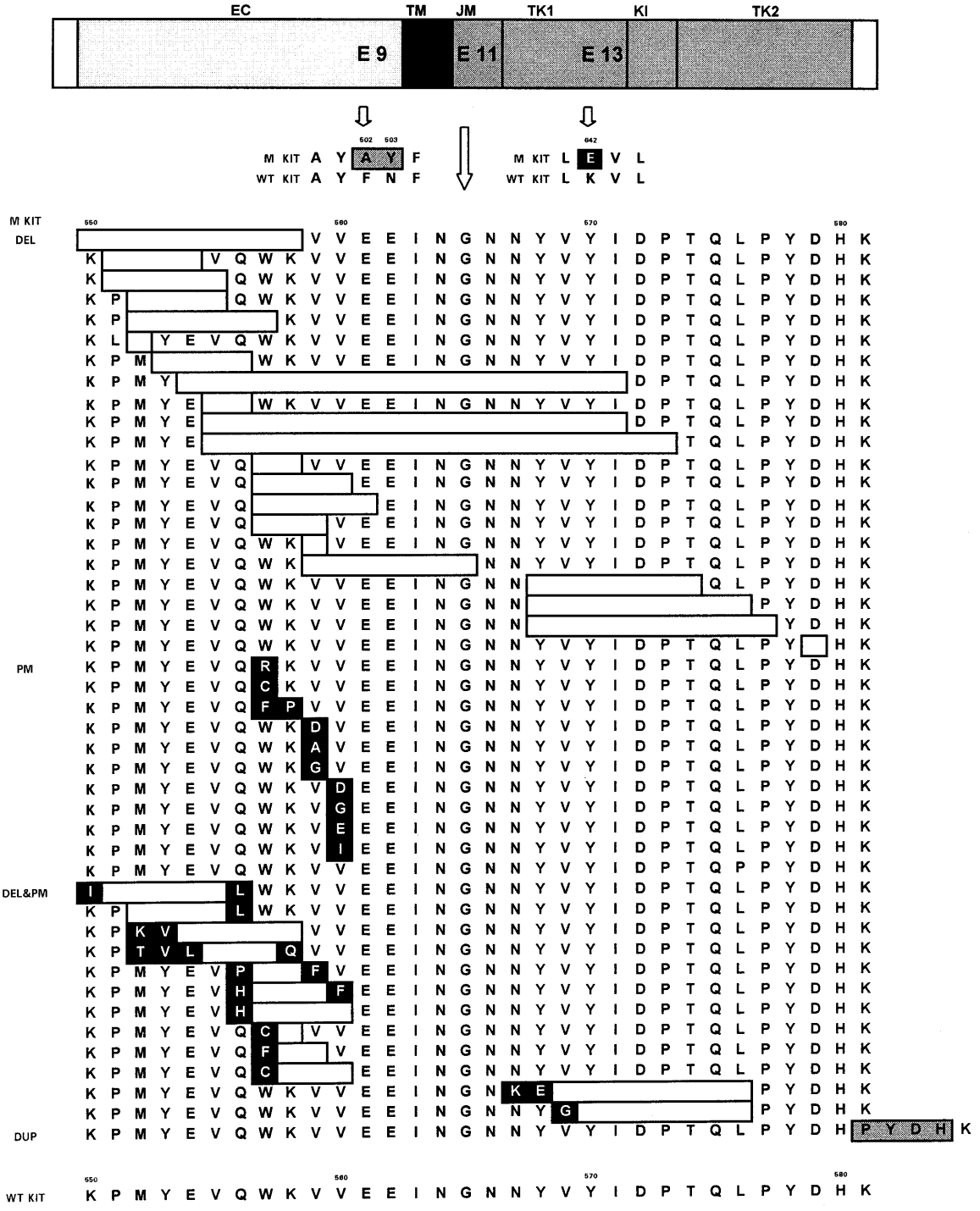

Fig. 3 Spectrum of amino sequences of mutated KIT (CD117, stem cell factor receptor). Schematic representation of KIT gene is shown above. The locations of involved exons (*E*) are shown within the domains of the gene. The deletions are shown as *empty boxes*, point mutations as *black boxes*, and insertions as *gray boxes*. The wild-type (*WT*) KIT amino acid sequence is shown below the mutant (*M*) sequences. The codon numbers are indicated above the sequences. *DUP* duplication; *DEL* deletion; *PM* point mutation; *EC* extracellular domain; *TC* transmembrane domain; *JM* juxtamembrane domain; *TK1* and *TK2* tyrosine kinase domains, *KI* kinase insert

cations may involve oncogenes. Although the extensive CGH studies on GISTs have so far not pinpointed directly to any involved genes, certain recurrent findings may have pathogenetic importance.

Among the most common losses typically found in both benign and malignant GISTs are losses in chromosome 14q and in chromosome 22q [10]. Mapping of allelic losses [loss of heterozygosity (LOH)] recently identified two areas with the highest frequency of losses at 14q21 and 14q23 [11]. Losses in chromosome 1p were characterized by O'Leary et al. [52]. The area of involve-

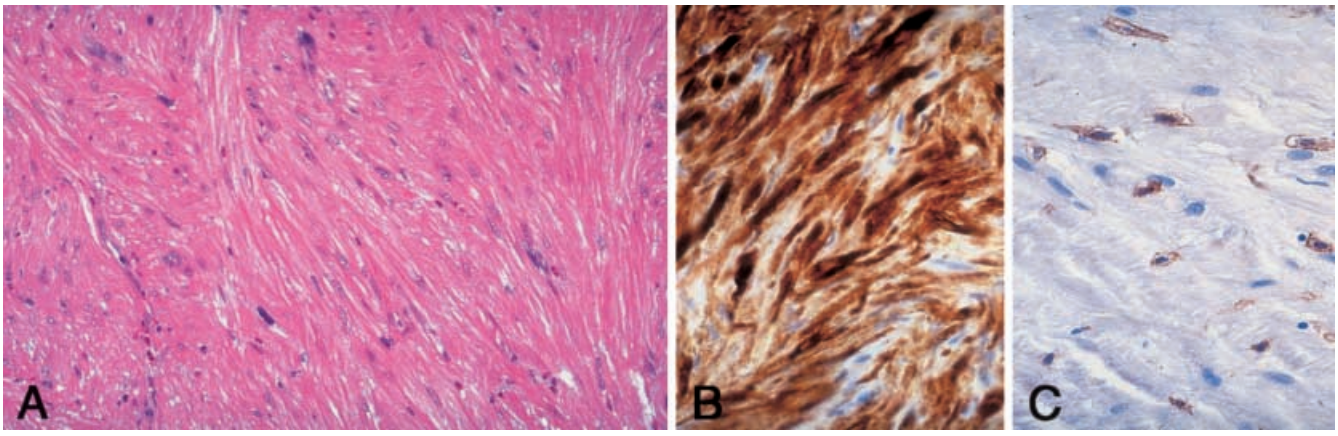

Fig. 4 Typical esophageal leiomyoma. **A** Histologically, the tumor is only moderately cellular with abundant eosinophilic cytoplasm. **B** The tumor cells are strongly positive for desmin. **C** The tumor cells are negative for KIT (CD117, stem cell factor receptor), but infiltrating mast cells are positive

ment, 1p36, was suggested to contain an as of yet unidentified tumor suppressor locus.

Comparison of benign and malignant GISTs has shown that DNA copy number gains in various loci predominantly occur in malignant GISTs, suggesting that the CGH evaluation could have a prognostic predictive value [12]. GISTs have been reported in connection with neurofibromatosis type 1 (NF1) [63], and some patients with NF1 have multiple GISTs, an otherwise very rare occurrence. A recent study suggested a non-random association of NF1 and GISTs [25]; the nature of this association and its possible relationship with the NF1 gene is unknown.

Relationship of GIST to GANT

Gastrointestinal autonomic nerve tumors (GANTs), originally described under the name "plexosarcoma", were identified based on electron microscopy (EM), where complex cell processes and neuroendocrine secretory granules were observed [22, 77]. Subsequently, a larger series showed a heterogeneous histological appearance quite similar to the spectrum of GISTs [30]. We have seen a small number of tumors that have the ultrastructural features of GANTs and are KIT positive. Although larger series have not been studied as of yet, the entities of GANT and GIST seem to merge, i.e., GANTs represent an ultrastructural subset of GISTs. This is also indirectly supported by the EM data, which finds autonomic nerve-like differentiation in a substantial proportion of GISTs [15]. Correlative histological, ultrastuctural, and molecular genetic studies on a large number of tumors diagnosed as GANTs are needed to confirm that GANTs represent a subset of GISTs.

True leiomyomas

Leiomyoma occurs chiefly in the esophagus, colon, and rectum within the GI tract. It is the most common mesenchymal tumor of the esophagus but is very rare in the stomach and nearly non-existent in the small intestine. Peculiar leiomyomas limited to the muscularis mucosae occur in the colon and rectum as small intraluminal polyps.

The esophageal leiomyomas present more often in males (2:1) and occur at a younger age than GISTs, with the median age of 30–35 years. Most of the esophageal leiomyomas occur in the lowest third, where they manifest by dysphagia. As many as half may be asymptomatic incidental chest X-ray findings. The esophageal leiomyomas are typically intramural tumors that may be spherical or oval or longitudinally extending as sausage-shaped, or circumferentially as U-shaped masses. Although they are usually 1–3 cm in diameter, some leiomyomas have reached a large size (>500 g, >10 cm) [41, 65]. Similar tumors rarely occur in the stomach, especially in the cardia.

Histologically, leiomyomas are paucicellular spindle cell tumors with low or moderate cellularity and slight if any mitotic activity. Focal nuclear atypia may be present. The cells have elongated nuclei and eosinophilic, fibrillary, often clumped cytoplasm (Fig. 4). Calcifications are sometimes present. Esophageal leiomyomas are typically strongly positive for both desmin and SMA and are negative for CD34 and KIT and c-kit mutations [41].

Deletions and rearrangements of the genes encoding $\alpha 5$ and $\alpha 6$ chains of collagen type IV have been reported in esophageal leiomyomatosis and recently also in sporadic esophageal leiomyoma. Alterations in the collagen type-4 genes are significant candidates for the pathogenetic mechanism of this tumor [21, 64, 80]. Esophageal leiomyomatosis may occur together with Alport's syndrome, which is a renal glomerular basement membrane disease, where collagen type-IV abnormalities have been thought to be pathogenetically important [64, 80]. CGH studies have shown that esophageal leiomyomas do not show losses of chromosome 14, often seen in GISTs. Instead, they may show gains of chromosome 5 [62].

Leiomyomas of the muscular mucosae of the colon and rectum are small benign tumors that are typically in-

cidental findings at colorectal endoscopy in older adults. These tumors merge with the smooth muscle of the muscularis mucosae and are small, usually less than 1 cm. They are composed of well-differentiated smooth muscle cells that are positive for SMA and desmin and negative for KIT and CD34. Leiomyomas resembling the uterine ones may be attached to the external aspect of the sigmoid and rectum. Similar to uterine leiomyomas, these tumors are composed of well-differentiated, desmin and muscle actin positive cells that are typically also positive for the estrogen receptor and negative for KIT [44].

True leiomyosarcomas of the GI tract

Our review of mesenchymal tumors of the GI tract, including all esophageal and colorectal mesenchymal tumors, has revealed a small number of well-differentiated malignant smooth muscle tumors that correspond to typical leiomyosarcomas, such as the vascular and retroperitoneal ones. Like GISTs, these tumors typically occur in older individuals. In contrast to GISTs, true leiomyosarcomas seem to be more often intraluminal polypoid tumors, possibly suggesting their origin from the inner smooth muscle layers or from the muscularis mucosae of the colon [43]. Histologically, the leiomyosarcomas are composed of well-differentiated smooth muscle cells with cigar-shaped nuclei and well-differentiated cytoplasm. They are negative for KIT and CD34 and are positive for SMA and usually for desmin. The lack of KIT mutations in these tumors suggests that the leiomyosarcomas are not extreme phenotypic variants of GISTs but have a different pathogenesis. More cases need to be studied to confirm this.

Schwannoma

Schwannomas are rare in the GI tract and are outnumbered by GISTs, approximately by 50–100:1. They most commonly occur in the stomach and occasionally in the esophagus and intestines. GI schwannomas are not associated with NF1 and NF2. Similar to GISTs, schwannomas predominantly occur in older middle age (average 58 years in the largest series) [8, 60]. They may grossly and clinically resemble GISTs. The schwannomas are usually covered by intact mucosa and principally involve the submucosa and muscularis propria. The tumors vary from 0.5–7 cm (mean 3 cm) in diameter and are spherical or ovoid, occasionally with a multinodular pattern similar to plexiform schwannoma. Histologically, the GI schwannomas usually show a slender, vaguely bundled S100-protein positive spindle cells in fibrous, S100 protein negative background. The tumors often have sprinkled lymphocytes and show a lymphoid cuff which sometimes has germinal centers. Malignant counterparts of GI schwannomas have not been documented.

Other gastrointestinal mesenchymal tumors that are not GISTs

Although GISTs form the majority of primary mesenchymal tumors of the GI tract, there are other tumors potentially simulating GISTs which are histogenetically and pathogenetically unrelated. These tumors have been summarized in Table 1. Intra-abdominal fibromatosis (desmoid) may form a mesenteric mass that also involves gastric and intestinal walls [4]. These tumors are usually less cellular and more collagenous than GISTs, and they are negative for KIT and in most cases also for CD34 but may be variably positive for actins and desmin [47, 61].

Inflammatory fibroid polyp usually occurs in the stomach or small intestine and less commonly elsewhere in the GI tract. It is a somewhat heterogeneous group of spindle cell lesions, some of which are highly vascular, granulation tissue-like, and others are composed of slender spindle cells concentrically arranged around blood vessels. The tumor cells in the latter variant are often positive for CD34, but all fibroid polyps are negative for KIT [20, 44, 76].

Table 1 KIT (CD117, stem cell factor receptor)-negative tumors that may simulate gastrointestinal stromal tumors (GISTs) clinically, grossly, or histologically. *SMA* smooth muscle actin

Entity	Similarities and differences from GIST
Esophageal leiomyoma	Paucicellular, composed of well-differentiated smooth muscle cells. Positive for desmin and SMA
Uterine-type leiomyoma	Usually pelvic, in young to middle-aged women. Positive for desmin, SMA, and estrogen and progesterone receptors
True leiomyosarcoma	Composed of well-differentiated smooth muscle cells, positive for desmin and SMA. Often presents as a polypoid intraluminal tumor
Inflammatory fibroid polyp	Spindle cell lesion, often CD34 positive. Slender spindle cells, admixed lymphoid cells, and eosinophils
Inflammatory myofibroblastic	Often in children, may form a transmural tumor gastric or intestinal mass, but more often an omental or mesenteric mass
Mesenteric desmoid	May have GIST-like gastric or intestinal involvement. Grossly very firm. Fibroblasts and myofibroblasts in collagenous background, CD34 negative
Dedifferentiated liposarcoma	Mesenteric, retroperitoneal, and may involve intestinal walls. May have a lipomatous component or have myxoid or pleomorphic MFH-like or fibrosarcoma-like features
Schwannoma	Usually small, yellow circumscribed submucosal tumors. Slender, often bundled S100-protein positive spindle cells in S100-negative fibrous background

Inflammatory myofibroblastic tumor (IMT) often occurs in children, but it may also present in adults. It is synonymous to inflammatory pseudotumor (although this term has also been used in a generic sense) and with inflammatory fibrosarcoma (its hypercellular variant). This tumor may form a GIST-like transmural mass in the stomach or intestines, although it is more often omental or mesenteric. The spindled tumor cells are typically admixed with lymphocytes and plasma cells and are negative for KIT and CD34 [5, 36, 44].

Dedifferentiated retroperitoneal liposarcomas may be attached to the bowel wall and sometimes simulate GISTs. However, these tumors usually form a predominantly extramural mass and have a lipomatous component. If the lipomatous component is not included in the sampling, these tumors may be difficult to distinguish from GIST. According to our experience, dedifferentiated liposarcomas are negative for KIT [44].

The commonly KIT-positive mesenchymal tumors of the GI tract that are not GISTs, include metastatic melanoma and angiosarcoma. According to our experience, approximately half of these tumors express KIT [44]. Their other specific histological and immunohistochemical features allow for the differential diagnosis from GIST.

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