Gastrointestinal Stromal Tumors

A Review of the Literature

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• Gastrointestinal stromal tumors are mesenchymal neoplasms with a spectrum of histologic appearances and biologic activity. The morphologic classification of these lesions has evolved over time, and molecular analysis has led to a better understanding of their nature. The histologic differential diagnosis for these lesions is broad and includes many spindle cell lesions of the gastrointestinal tract, including neoplasms of true smooth muscle and neural origin, proliferating fibrous lesions, metastatic neoplasms, and primary sarcomas of vascular and adipose origin. Immunohistochemical studies that include CD117 have become invaluable in the classification of mesenchymal lesions arising in the gastrointestinal tract. Treatment of gastrointestinal stromal tumors has historically been involved surgery, but the use of the chemotherapeutic agent imatinib mesylate for advanced disease has made accurate classification even more important. The molecular features have not only allowed us to understand the pathogenesis of these tumors but also have proven to be associated with response to kinase inhibitors.

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In 1941, Golden and Stout[1] described a set of mesenchymal tumors arising in the bowel wall. Under the mistaken assumption that these tumors originated from smooth muscle cells, they designated them as leiomyoblastoma, leiomyoma, and leiomyosarcoma, based on their morphologic appearance.[1] In the late 1960s and early 1970s, electron microscopy revealed that few of these tumors had evidence of smooth muscle differentiation, an observation that was corroborated later with the addition of immunohistochemistry in the late 1980s.[2,3] Mazur and Clark[4] proposed the term *stromal tumors* for these mesenchymal lesions because it did not specify a line of differentiation. In 1984, Herrera et al[5] studied a subset of these tumors showing positivity for S100 protein by immunohistochemistry and evidence of schwannian and neuroaxonal differentiation by electron microscopy and proposed the name *plexosarcomas* for them. Later, they become known as *gastrointestinal autonomic nerve tumors*.

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CD34 was advocated as a more reproducible marker of gastrointestinal stromal tumors (GISTs). However, only 60% to 70% of GISTs are positive for this marker, and because a broad variety of spindle cell tumors, including smooth muscle and neural cell tumors, also express it, the specificity of CD34 was significantly reduced in the diagnosis of mesenchymal tumors of the gastrointestinal (GI) tract.

In the late 1990s, 2 main approaches were available for dealing with these lesions. One approach classified all mesenchymal tumors of the GI tract as GISTs, regardless of the immunohistochemical profile. The second approach excluded true smooth muscle and neural tumors in an attempt to identify a subset of mesenchymal tumors with unique clinicopathologic features. Although the second approach ultimately proved to be correct, initially its reproducibility was flawed by the lack of a sensitive and relatively specific diagnostic marker.[3]

This situation changed drastically in 1998, when Hirota and colleagues[6] discovered that most GISTs harbored *c-kit* mutations that resulted in full-length KIT proteins with ligand-independent activation. Furthermore, the authors[6] demonstrated that GISTs were usually positive for CD117 (*c-kit*) by immunohistochemistry. This single discovery changed our understanding of the pathogenesis of GISTs. Later, it became clear that a subset of GISTs harbored mutations in the platelet-derived growth factor receptor α (*PDGFRA*). The term GIST is currently applied to ''specific, generally CD117$^+$ and *KIT* or *PDGFRA* mutation-driven mesenchymal tumors of the gastrointestinal tract with a set of characteristic histologic features including spindle cells, epithelioid and rarely pleomorphic morphology'' according to the definition proposed by Miettinen et al[7] and agreed upon on the GIST workshop held at the National Institutes of Health in April 2001.[3]

CLINICAL FEATURES

Gastrointestinal stromal tumors constitute approximately 2% of all neoplasms of the GI tract, where they represent the most common mesenchymal tumor. The annual incidence is estimated at 4500 to 6000 new cases per year in the United States. These tumors equally affect female and male patients, with a wide age distribution, although more than 75% of the cases affect patients older than 50 years of age[8–10]; 5% of the lesions arise in the esophagus, 50% in the stomach, 25% in the small bowel, and 10% in the colon and rectum.[8,10] Among small-bowel GISTs, 67% are located in the jejunum and 37% in the ileum.[10] In 10% of cases, GISTs arise outside the tubal gut,

in locations such as the mesentery, omentum and retroperitoneum, and have been referred to by the acronym EGIST (extragastrointestinal stromal tumors).[2,3,7]

The presenting symptoms may include early satiety, bloating, and some form of gastrointestinal bleeding, either acute bleeding, such as hematemesis, or chronic, insidious bleeding, manifested clinically by fatigue and weakness secondary to iron deficiency anemia.[7–10] The spectrum of clinical presentation is broad and is mainly related to tumor size. Small tumors are usually identified incidentally during an abdominal surgery, whereas large tumors will generally be associated with some form of GI bleeding. For tumors arising in the stomach, the presenting symptom is bleeding in 55% of cases, mainly in the form of hematemesis, and upper abdominal pain or discomfort in 17% of the cases.[9] Other presenting symptoms for tumors located in the stomach include palpable masses, acute abdomen secondary to intraabdominal hemorrhage, gastric outlet obstruction, and dysphagia.[9] In 20% of cases, the tumor is incidentally detected in the gastric wall during laparotomy for other medical reasons. For tumors arising in the small bowel, the most common clinical presentation is GI bleeding, most often in the form of chronic insidious bleeding.[10] Another common form of presentation for tumors in this location is acute abdomen prompting emergency surgery. As with tumors arising in the stomach, many lesions of the small bowel are an incidental finding during an unrelated abdominal surgical procedure.[10]

PATHOLOGIC FEATURES

Grossly, GISTs are usually centered in the bowel wall but may extend to involve either the mucosal or the serosal surfaces. Tumor size ranges from 1 to 35 cm, with a median size of 5 cm. On cut sections, the tumors are gray-white and solid, with a fleshy appearance. Tumors of any size, but especially large tumors, can have areas of hemorrhage and necrosis resulting in a cystic appearance.[7–11] The gross appearance cannot be used to predict clinical behavior, although the size, presence of mucosal ulceration, and multinodularity are the most important gross parameters that should be recorded in every case.

Microscopically, tumors are well circumscribed but not encapsulated and will characteristically show a pushing, expansive interface with the surrounding tissues (Figure 1). Gastrointestinal stromal tumors are very cellular lesions, with 70% of cases composed of spindle cells, 20% of epithelioid cells, and the remainder having a mixed cellular composition. Spindle cells are usually arranged in interlacing, short fascicles or in a short, storiform pattern of growth. The spindle cells are monomorphic, with rounded to elongated nuclei showing fine, open chromatin, inconspicuous nucleoli, and abundant pale-pink fibrillary cytoplasm with indistinct cell borders and a syncytial appearance (Figure 2). Epithelioid cells are usually arranged in cohesive nests and diffuse sheets with scant interposed stroma. The epithelioid cells are polygonal with round, centrally located nuclei displaying small nucleoli and moderate amounts of amphophilic cytoplasm with prominent cell borders (Figure 3). Most cases will have a small amount of intervening stroma that can show hyalinization or myxoid changes. In general, stromal collagen deposition is minimal, and the mitotic rate is variable. Although marked cellular pleomorphism has been described in up to 2% of cases, diffuse cellular pleomorphism in a GIST would be unusual and more suggestive of a true smooth-muscle tumor.[2,3,11] Epithelioid lesions occur far more commonly in the stomach than in the small bowel.[9,10] When they arise in the small bowel, epithelioid GISTs have a tendency to adopt a so-called paraganglioma-like pattern, which has been associated with unfavorable prognosis.[10] Nuclear palisading is present in up to 50% of gastric spindle cell GISTs and 70% of small-bowel lesions and has been associated with a favorable clinical outcome[9,10] (Figure 4). A peculiar but rare feature most often seen in gastric tumors is the presence of juxtanuclear cytoplasmic vacuoles. Up to 44% of small-bowel GISTs show the presence of skenoid fibers, hyaline or fibrillar, brightly eosinophilic structures, typically positive for periodic acid–Schiff, which appear to be composed of nodular tangles of collagen fibers.[3,7,10] The presence of skenoid fibers has been associated with a favorable clinical outcome.[10] More than one-half of the so-called EGISTs have an epithelioid morphology and are similar to gastric GISTs in relation to mutational status.

IMMUNOHISTOCHEMICAL FEATURES

By immunohistochemistry, 90% to 95% of GISTs will be diffusely and strongly positive for CD117 (c-Kit), with a cytoplasmic, membranous, or paranuclear ''dotlike'' distribution pattern. A few cases show only focal staining of the neoplastic cells. Although the prognostic and therapeutic implications of this focal staining pattern are not yet clear, it might give rise to false-negative results, especially when dealing with small endoscopic biopsies. Not all $CD117^+$ tumors are GISTs. Malignant melanomas, synovial sarcomas, mesenteric fibromatosis (desmoid tumors), and schwannomas have been reported as positive for this marker. Factors related to the immunoperoxidase preparation, such as the type and dilution of the antibody and the antigen retrieval technique used, are known to produce false-positive results for CD117.[11,12] In view of the predictive value of CD117 immunostaining in the context of mesenchymal tumors of the GI tract, strict application of quality-control protocols is mandatory to minimize false-positive and false-negative results.[3] Detailed attention to built-in negative and positive controls is critical when interpreting a CD117 immunostain. Optimal CD117 immunostains should highlight normal interstitial cells of Cajal and mast cells, whereas smooth muscle cells and fibroblasts should exhibit completely negative findings. The need for negative internal controls should be kept in mind at the time of selecting the appropriate paraffin block for performing immunohistochemical stains. Even following adequate immunoperoxidase techniques, around 5% of GISTs will be negative for CD117.[12] Some $CD117^-$ GISTs have epithelioid morphology and arise in the stomach or omentum. Approximately 80% of $CD117^-$ GISTs harbor *PDGFRA* mutations, whereas most of the remaining cases will prove to harbor *KIT* mutations.[11,12] The extent and pattern of CD117 immunostaining cannot be used to predict the type of mutation present in any given tumor.[12] The diagnosis of $CD117^-$ GISTs can be particularly problematic, more so when there is also focal staining for smooth muscle markers.

Immunophenotyping for CD117 alone is insufficient for the diagnosis of GISTs; a panel of immunostains is required.[13] CD34 is positive in 60% to 70% of GISTs, whereas S100 protein stains up to 5% of these tumors. Smooth muscle actin is expressed in 30% to 40% of the cases, and

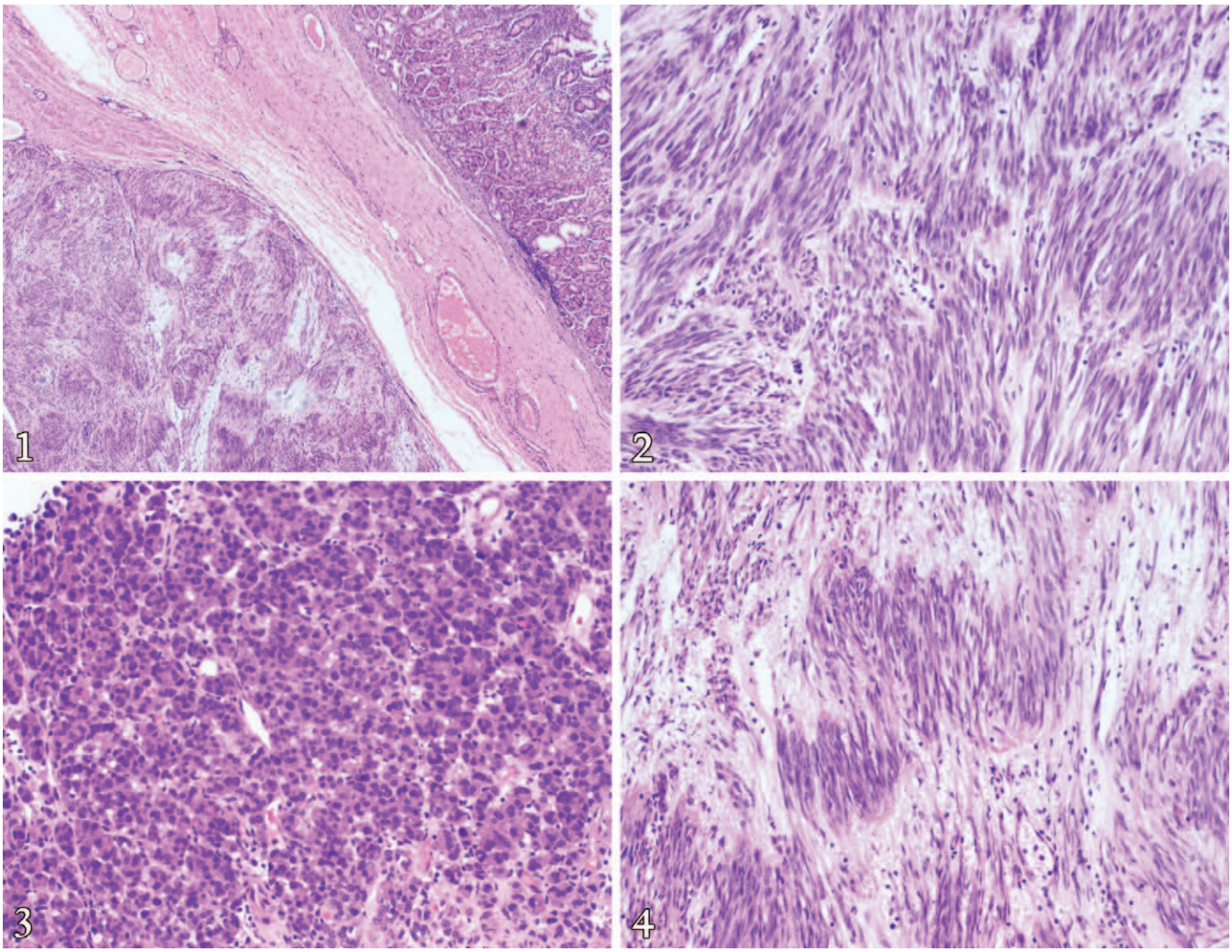


Figure 1. *Spindle cell gastrointestinal stromal tumor arising in the stomach showing a pushing border with no significant inflammatory infiltrate (hematoxylin-eosin, original magnification ×40).*

Figure 2. *Gastric spindle cell gastrointestinal stromal tumor displaying interlacing fascicles of monomorphic spindle cells with elongated nuclei (hematoxylin-eosin, original magnification ×200).*

Figure 3. *Epithelioid gastric gastrointestinal stromal tumor composed of nests and cords of polygonal cells with a moderate amount of eosinophilic cytoplasm and rounded nuclei (hematoxylin-eosin, original magnification ×200).*

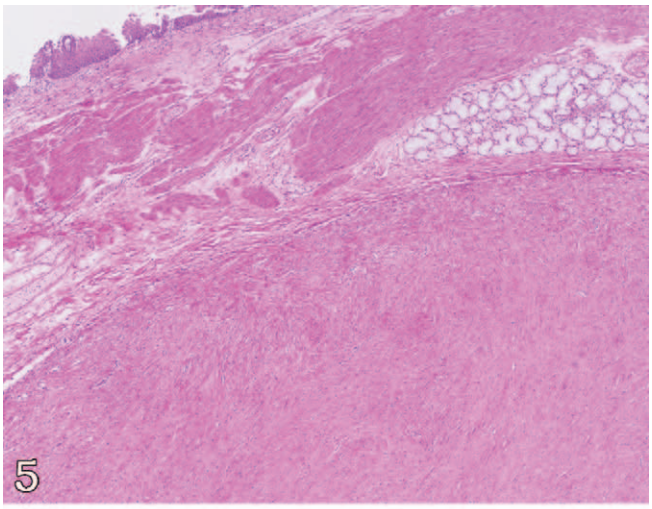
Figure 4. *Spindle cell gastrointestinal stromal tumor of the gastric wall showing prominent nuclear palisading (hematoxylin-eosin, original magnification ×200).*

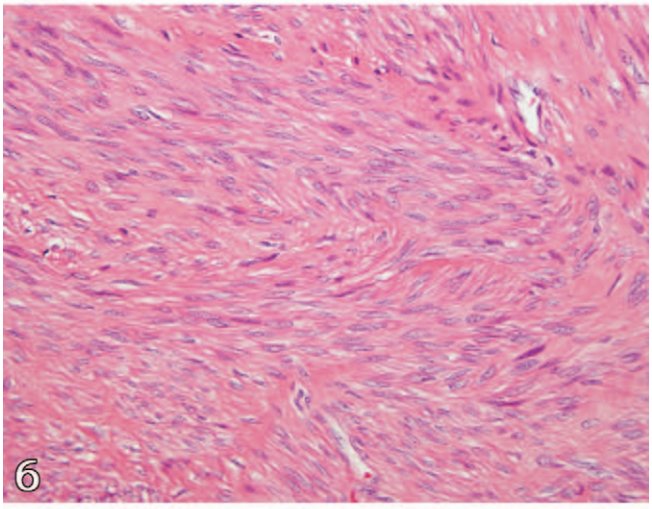
1% to 2% of cases are positive for desmin. The aforementioned smooth muscle markers are usually weak, with a focal distribution pattern. h-Caldesmon is positive in 85% of GISTs and may be useful to support the diagnosis in CD117$^-$ tumors.[12]

A promising protein known as DOG1, discovered using gene expression profiling studies, has emerged as a sensitive and specific marker that can be especially useful in the setting of CD117$^-$ GISTs.[14] In a large study comparing DOG1 expression with CD117, the authors[14] found that overall, 87% of GIST were positive for DOG1, whereas only 74% of them expressed CD117. Interestingly, 79% of GISTs harboring a *PDGFRA* mutation were positive for this marker, whereas only 9% expressed CD117. It appears that DOG1 expression is not related to mutational status in GISTs, and it may be a useful marker to identify a subset of patients with CD117$^-$ GISTs, who might benefit from targeted therapy.

Gene expression profile studies revealed that protein-kinase θ is highly expressed in these tumors, and currently available antibodies to this protein are highly sensitive and specific for the diagnosis of GIST, with the exception of positive staining in up to 14% of schawnnomas.[2,11,15] The expression of this marker does not appear to be related to the mutation status. Moreover, all CD117$^-$ GISTs harboring *PDGFRA* mutations were positive for protein-kinase θ in one study.[15] Since the original publication, several studies have corroborated the role of protein-kinase θ in the diagnosis of these tumors, especially in the context of CD117$^-$ GISTs.[15–18] On the other hand, currently available antibodies directed to *PDGFRA* do not show reproducible results in paraffin-embedded sections and are not currently suitable for clinical use.[8,12]

Although the term *GIST* should apply only to neoplasms that are CD117$^+$, rare exceptions were accepted during the 2001 consensus conference. Such exceptions in-





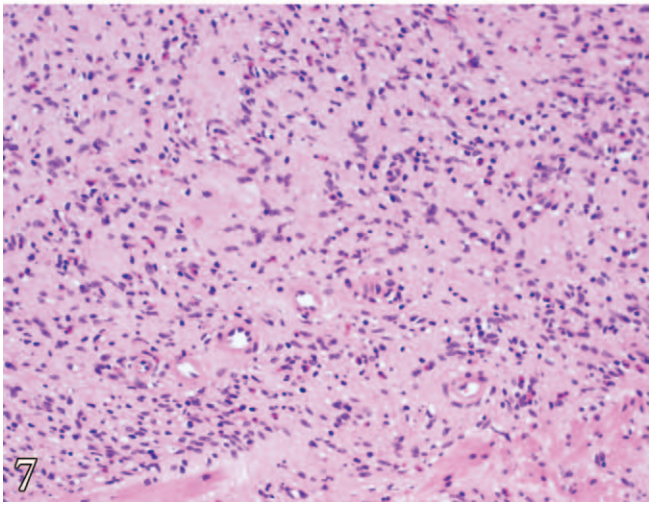


Figure 5. *Leiomyoma of the esophagus composed of spindle cells with elongated, cigar-shaped nuclei (hematoxylin-eosin, original magnification ×100).*

Figure 6. *Higher magnification of a leiomyoma of the esophagus showing spindle cells in fascicles with elongated nuclei and moderate amount of eosinophilic cytoplasm (hematoxylin-eosin, original magnification ×400).*

Figure 7. *Inflammatory fibroid polyp of the stomach displaying spindle cells, surrounding thickened, granulation-type blood vessels, and associated with a dense inflammatory infiltrate containing many eosinophils (hematoxylin-eosin, original magnification ×200).*

clude tumors with the typical cytoarchitectural features but which (1) are completely inert to immunoperoxidase stains probably because of fixation artifact; (2) are found to be negative because of sampling issues, such as small endoscopic biopsies with adequate internal controls for others antigens; (3) have ceased to express CD117 because of some form of clonal evolution; or (4) belong to the small percentage of tumors that lack either *KIT* mutations or *KIT* overexpression. According to the consensus recommendations, mesenchymal tumors of the GI tract in any of these situations should be labeled *spindle (epithelioid) stromal neoplasm most consistent with GIST.*[3] Also, according to the consensus approach, CD117 should be performed in every case, as a confirmatory measure, to improve diagnostic standardization and to help determine patient eligibility for imatinib mesylate (Novartis, Basel, Switzerland) therapy (see below).[3]

DIFFERENTIAL DIAGNOSIS

Many tumors enter the differential diagnosis of GISTs. The realization that most GISTs have the potential for adequate response to a new, targeted therapy has increased the pressure on pathologists to properly differentiate these tumors from potential mimics. Careful morphologic evaluation, along with the results of a small immunoperoxidase panel, should be sufficient in most cases. However, morphology can be misleading, especially in epithelioid tumors, and some of the tumors that enter the differential diagnosis are known to be positive for CD117. In these cases, the use of additional antibodies or the performance of mutational studies can be important.

True Smooth Muscle Tumors

With the exception of the esophagus and colon, true smooth muscle tumors of the GI tract are actually quite rare. Intramural leiomyomas are particularly common in the esophagus, where they outnumber GISTs. Esophageal leiomyomas most commonly arise from the muscularis propria and may become large enough to be associated with dysphagia.[9] Conversely, colorectal leiomyomas usually arise from the muscularis mucosae and present as small, asymptomatic polyps, commonly discovered during a screening colonoscopy.[11–13] Grossly, esophageal leiomyomas present as firm, whorled, white nodule of varying sizes. Microscopically, these tumors are well circumscribed but not encapsulated, are less cellular than GISTs, and are composed of spindle cells with cigar-shaped nuclei and eosinophilic cytoplasm arranged in interlacing fascicles (Figures 5 and 6). Up to 24% of esophageal leiomyomas can have an epithelioid morphology.[13] The stroma may show areas of hyalinization and may characteristically contain many mast cells. By immunohistochemistry, the neoplastic cells are strongly and diffusely positive for smooth muscle actin and desmin and negative for CD34 and CD117. An important source of error in the evaluation of CD117 immunoperoxidase stains is that entrapped mast cells show positive staining. Esophageal leiomyomas are benign tumors, generally amenable to surgical resection, in contrast to esophageal GISTs, which have a tumor-related mortality rate of 53%.[9]

Mesenteric Fibromatosis (Desmoid Tumors)

Mesenteric fibromatosis most commonly arises in the mesentery and omentum of middle-aged adults but can subsequently involve the wall and/or lumen of the gut,

mimicking a GIST.[11,19] It is important to remember that GISTs can arise outside the tubal gut, and therefore, gross distinction between the 2 processes could be unreliable. Grossly, mesenteric fibromatosis presents as white, firm masses, ranging from 10 to 20 cm. Microscopic evaluation reveals a hypocellular lesion composed of spindle to stellate tissue culturelike fibroblasts arranged in parallel, in a collagenous background, with elongated and dilated thin-walled veins and a sparse perivascular lymphocytic infiltrate. Characteristically, these lesions have a ''melting insinuation'' interface with the surrounding tissues, in contrast to the expanding, pushing border of GISTs. Desmoid tumors are negative for CD34 and CD117 but can display focal positivity with smooth muscle actin and desmin. Cytoplasmic positivity for CD117 has been reported in up to 75% of cases of mesenteric fibromatosis; these results depend strongly on the antibody used, the dilution, and the antigen-retrieval technique, suggesting a false-positive result.[13] Further optimization and standardization of the immunoperoxidase technique has shown very low levels (5%) of CD117 positivity in desmoid tumors.[13] In doubtful cases, demonstration of β-catenin may be helpful in identifying desmoid tumors as nuclear positivity for this marker has been identified in up to 90% of cases. It is important to be aware that cytoplasmic positivity for β-catenin is not diagnostic because it can be seen in other tumors, including GISTs.[20] The distinction between mesenteric fibromatosis and GIST is clinically important for at least 2 reasons: First, desmoid tumors, unlike GISTs, do not have the capacity to metastasize although they can recur locally, and more important, up to 10% of cases of mesenteric fibromatosis happen in the setting of familial adenomatous polyposis, mandating patient testing for this condition.[13]

Inflammatory Fibroid Polyp

This is a benign polypoid lesion that most commonly arises in the gastric antrum but may also manifest as an intraluminal mass in the small bowel associated with intestinal obstruction. Microscopically, these are submucosal lesions composed of spindle and stellate stromal cells in a granulation-type or fibromyxoid stroma with thickened blood vessels and a dense inflammatory infiltrate (Figure 7). The spindle cells tend to condense around blood vessels to form whorled, perivascular cuffs. Prominent eosinophils are a characteristic finding but the inflammatory infiltrate also includes lymphocytes, plasma cells, macrophages, and mast cells. By immunohistochemistry, the stromal cells have been reported to express CD34, fascin, cyclin D1, CD35, and calponin but are negative for CD117.[11,13] The mast cells present in the lesion can express CD117 and be a potential source of error in the interpretation of the immunostains.

Inflammatory Myofibroblastic Tumor (Inflammatory Pseudotumor)

The prototypic case of inflammatory myofibroblastic tumor occurs in the abdomen of a child or young adult, more commonly as an omental or mesenteric mass.[11,19] Microscopically, it shows a more heterogeneous cellular composition than a GIST, being composed of a proliferation of elongated spindle cells with amphophilic cytoplasm admixed with many lymphocytes and plasma cells. The presence of abundant plasma cells in a spindle cell proliferation in the abdominal cavity of a young patient should raise the differential diagnosis of inflammatory myofibroblastic tumor. The spindle cells are variably positive for smooth muscle actin and desmin and negative for CD34 and CD117. In up to 60% of the cases, positivity for ALK-1 has been described in the spindle cells. Most cases pursue a benign clinical course, but as many as 25% will recur locally.

Schwannomas

Gastrointestinal schwannomas are outnumbered by GISTs in the GI tract by approximately 50:1 and represent around 6% of all GI mesenchymal neoplasms.[11,13,21,22] These benign tumors affect adults between 60 and 70 years of age and most commonly arise in the stomach, followed by the colon. The gross features do not allow for a clear separation from GISTs because both are intramural, well-circumscribed tumors of varying size that may have areas of necrosis and ulceration of the overlying mucosa. Microscopically, schwannomas are moderately to highly cellular tumors, composed of interlacing fascicles of spindle cells, with wavy, tapered nuclei interspersed among parallel collagen strands, or a myxoid stroma with scattered inflammatory cells. One low-power microscopic feature that should alert the pathologist to the diagnosis is the presence of a dense, peripheral lymphoid cuff often containing prominent germinal centers, an unusual feature in GISTs. Unlike soft-tissue schwannomas, nuclear palisading and hyalinized blood vessels are not commonly present in GI schwannomas.[13,19,21,22] In the end, accurate differentiation rests on immunohistochemistry. Gastrointestinal schwannomas are strongly and diffusely positive for S100 protein, and unlike soft-tissue schwannomas, many cases will show positive staining with glial fibrillary acidic protein.[11] Typically, they are negative for CD117, smooth muscle actin, and desmin, although occasionally they can show positive staining for CD34.

Solitary Fibrous Tumors

Solitary fibrous tumors are uncommon neoplasms derived from submesothelial cells that commonly occur in the pleural cavity. Their rare occurrence in the abdominal cavity may explain their tendency to be misdiagnosed as the more commonly encountered GISTs. Grossly, they present as firm, well-circumscribed, whorled masses of the peritoneum or retroperitoneum that occasionally appear to be attached to the bowel wall.[13,19] Solitary fibrous tumors are composed of bland spindle to oval cells with a characteristic patternless pattern of growth that can occasionally be fascicular or storiform. The spindle cells are admixed with gaping, staghorn vessels and variable numbers of hyalinized collagen fibers. By immunohistochemistry, these tumors are positive for CD34 and CD99 and negative for CD117. Unfortunately, CD99 is not helpful in the differential diagnosis with GISTs because almost all GISTs will show positive staining for this marker.[13] Solitary fibrous tumors will usually behave in a benign fashion although malignant examples have been reported.

Other Tumors

Occasionally, some other tumors should be considered in the differential diagnosis of mesenchymal tumors of the GI tract, including malignant melanoma, angiosarcoma, dedifferentiated liposarcoma, and sclerosing mesenteritis. Malignant melanomas and angiosarcomas rarely occur in the GI tract, but they can be composed of spindle or epi-

Proposed Risk Assessment Scheme for Predicting Aggressive Clinical Behavior in Gastrointestinal Stromal Tumors According to Mitotic Index, Size, and Site[a]

Mitotic Index, HPF	Size, cm	Risk for Progressive Disease[b] (%)			
		Gastric	Duodenum	Jejunum/Ileum	Rectum
≤5/50	≤2	None (0)	None (0)	None (0)	None (0)
≤5/50	>2, ≤5	Very low (1.9)	Low (8.3)	Low (4.3)	Low (8.5)
≤5/50	>5, ≤10	Low (3.6)	Insufficient data	Moderate (24)	Insufficient data
≤5/50	>10	Moderate (12)	High (34)	High (52)	High (57)
>5/50	≤2	None (0)[c]	Insufficient data[c]	High[c] (50)	High (54)
>5/50	>2, ≤5	Moderate (16)	High (50)	High (73)	High (52)
>5/50	>5, ≤10	High (55)	Insufficient data	High (85)	Insufficient data
>5/50	>10	High (86)	High (86)	High (90)	High (71)

Abbreviation: HPF: high power field.

[a] Reprinted from [31]Miettinen M, Lasota J. Gastrointestinal stromal tumors: pathology and prognosis at different sites. *Seminars in Diagnostic Pathology.* 2006;23(2):70–83 with permission from Elsevier Ltd, Oxford, United Kingdom.

[b] Defined as metastasis or tumor-related death.

[c] Denotes few cases.

thelioid cells morphologically resembling GISTs and can show positive staining with CD117,[11,21] highlighting the importance of expanding the immunoperoxidase panel in the evaluation of mesenchymal lesions of the GI tract. Fortunately, most tumors that have been reported as positive for CD117 do not usually enter the morphologic differential diagnosis of GISTs.[11] Seminomas and dysgerminomas are known to express CD117, and they can potentially be considered in the differential diagnosis of retroperitoneal lesions.

PROGNOSTIC FACTORS, RISK STRATIFICATION, AND CLINICAL OUTCOME

There is general agreement that tumor size and mitotic count are the most important prognostic factors in GISTs. Other pathologic features that have been evaluated but have not been shown to predict the clinical course include cellularity, mucosal ulceration, and the presence or absence of *KIT* and/or *PDGFRA* mutations.[2,7,8,10,23] With prolonged clinical follow-up, it seems that any GIST has the potential to behave in a malignant fashion, and when they recur either in the abdominal cavity or give rise to liver metastases, prognosis is poor.[3,23] Based on the available data, the use of a risk assessment scheme for these lesions would appear to be more useful than following a set of criteria to classify GISTs as benign or malignant. For any given tumor, the 2001 consensus conference suggested reporting the risk of such tumors pursuing an aggressive clinical course.[3,24] The guidelines are valid for untreated tumors, and they have been updated after the publication of large series of GISTs, which showed that gastric tumors tend to behave in a less-aggressive fashion than small-bowel tumors of similar size and mitotic activity (Table).[3,8,9,12,24] Although less data are currently available for tumors arising in other locations, they should probably be stratified along with small-bowel tumors.

Most commonly, metastases from GISTs have been detected in the abdominal cavity with the next most common location being the liver. To date, no lymph nodes or lung metastases have been reported. Because these tumors have a well-recognized risk for late relapse, all patients with GISTs should be carefully and regularly followed for an indefinite period.[3,8]

Pathogenesis and Molecular Features

Interstitial cells of Cajal are unique pacemaker cells interposed between the autonomic nervous system and the muscular wall of the GI tract and are responsible for coordinated peristalsis. These cells have immunophenotypic and ultrastructural features of smooth muscle and neuronal cells in different proportions. Interestingly, cells with features of interstitial cells of Cajal have been described beneath the mesothelial lining of the omentum and mesentery.

c-Kit is a type III transmembrane tyrosine kinase receptor that has been implicated in the development and maintenance of red blood cells, mast cells, melanocytes, germ cells, and interstitial cells of Cajal. KIT expression appears to play a key role in committing primitive mesenchymal cells of the gut toward interstitial cells of Cajal differentiation. Binding of its ligand, known as *stem cell factor*, to the extracellular portion results in autophosphorylation of several tyrosine residues and activation of the Kit receptor. Upon activation, KIT phosphorylates other transduction proteins, resulting in modification of several cellular functions including adhesion, migration, and differentiation. Different *KIT* mutations have been implicated in several human tumors, including GISTs.

KIT mutations are identified in 85% to 95% of GISTs,[2,12,24] all of them resulting in full-length KIT proteins with ligand-independent activation. The mutations tend to cluster only in 4 exons: exon 9 (extracellular domain), exon 11 (intracellular juxtamembrane domain), exon 13 (split kinase domain), and exon 17 (kinase activation loop). Exon 11 mutations are the most common, being present in 60% to 70% of the cases and do not appear to be associated with any particular tumor location, size, or clinical outcome. On the other hand, exon 9 mutations are present in 10% of cases and appear to be associated with small-bowel tumors and a more aggressive clinical behavior. Exon 13 and 17 mutations are rare, each representing approximately 1% of the cases.[2,12,24]

Approximately 5% to 10% of GISTs harbor *PDGFRA* mutations involving exons 12, 14, and 18 that are homologous to *KIT* exon 11, 13, and 17. As with *KIT* mutations, all *PDGFRA* mutations result in ligand-independent activation of a similar signal-transduction pathway.[2] *KIT* and *PDGFRA* mutations are mutually exclusive.[2,12,19,24] Nearly all *PDGFRA*-mutant GISTs are located in the stomach, have an epithelioid morphology, and appear to be less clinically aggressive.[24–26] CD117 expression in *PDGFRA*-mutant tumors is often weak and focal or entirely negative.[12,25,26]

Currently, a group of tumors representing approximately 5% of GISTs do not harbor either *KIT* or *PDGFRA* mutations and are known as ''wild-type'' GISTs. Although negative for *KIT* mutations, these tumors can be positive for CD117 by immunohistochemistry.[12,24]

Therapeutic Considerations

The mainstay of treatment for primary GISTs is surgical resection, when possible. Until a few years ago, the available treatment options for recurrent or unresectable tumors were very limited. However, the US Food and Drug Administration has approved the use of imatinib mesylate for the treatment of recurrent and/or metastatic GISTs after several reports showed smaller and fewer metastases in 54%, and stable disease in 28%, of treated patients.[2,12] Imatinib mesylate is an Abl-kinase inhibitor originally developed for the treatment of chronic myelogenous leukemia that works as an adenosine triphosphate analog, binding to the intracellular portion of the Kit receptor, inhibiting signal transduction.[12]

The clinical response to this chemotherapeutic agent appears to be related to mutation status. Based on in vitro studies and pharmacologic trials, the *KIT* mutant isoforms are sensitive to the kinase inhibitor imatinib, whereas the most common *PDGFRA* mutations present in GISTs are usually completely resistant to it.[24,27] Nonetheless, up to one-third of *PDGFRA*-mutant GISTs would be sensitive to imatinib.[24,27,28] In several pharmacologic trials, the specific kinase genotype had a significant predictive value for the response to chemotherapy with imatinib. Patients with exon 11–mutant GIST have superior progression-free survival and overall survival than patients with exon 9–mutant or wild-type GISTs.[2,12,24,27] In addition, there appears to be a significant difference in dose sensitivity for exon 9–mutant GIST, and some would recommend dose adjustment based on the presence or absence of exon 9 mutation.[24]

Mutational analysis is not a current requirement of the GIST workup. However, several studies have shown that the type of mutation present is not only related to clinical response to these agents but also can be helpful in selecting the appropriate doses.[24] Currently, polymerase chain reaction techniques are available for *KIT* mutation analysis and represent a fast, sensitive, and relatively inexpensive method, the use of which can be prognostically important.[23] Although not specifically required at this time, the National Comprehensive Cancer Network task force strongly encourages the use of mutational analysis if treatment with imatinib is begun for unresectable or metastatic disease.[24]

A subset of patients treated with imatinib experience continued tumor growth within the first 6 months of treatment. The mechanisms involved in this type of primary resistance remain largely unknown, but a significant proportion of these cases will prove to be *KIT* exon 9–mutant GIST, wild-type GIST, or *PDGFRA* D842V–mutant GIST.[24,29] Patients who show initial clinical response to imatinib beyond 6 months, and then experience tumor progression are considered to have secondary resistance. Approximately 80% of secondary resistance is associated with the development of new kinase mutations that interfere with drug binding.[2,24,29] Notably, all secondary mutations appear to affect GIST with an underlying *KIT* mutation, especially those located at exon 11.[29] Although it is not clear which management option is better, current recommendations for patients with secondary imatinib resistance include increasing dosage or switching to another kinase inhibitor.[24]

A second tyrosine inhibitor, sunitinib, has been recently approved by the US Food and Drug Administration for patients with advanced GISTs who either have disease progression while on treatment with imatinib mesylate or have become intolerant to it.[12,24,30]

The role of imatinib in the adjuvant or neoadjuvant setting is uncertain at this point. However, the National Comprehensive Cancer Network guidelines recommend the use of neoadjuvant therapy with imatinib for patients with large or poorly positioned tumors that are considered to be marginally resectable.[24]

SUMMARY

In summary, GISTs represent mesenchymal lesions of uncertain histogenesis that display a wide spectrum of biologic behavior. The data that are currently available suggest that the most significant factors for predicting the clinical course of these lesions are tumor size and mitotic activity, and a risk assessment scheme has been proposed based on these parameters. Although treatment options have been traditionally limited to surgical resection, the use of imatinib mesylate for the treatment of unresectable disease has shown promise. Given the wide differential diagnosis of spindle cell lesions of the GI tract, accurate histologic classification of GISTs is necessary for appropriate therapy. In that regard, immunohistochemistry is a widely available and reliable tool. Considering the overlapping morphologic features of mesenchymal lesions of the GI tract, a panel of antibodies should be used, including CD117. Because of the availability of a targeted therapy, CD117 should be performed in every case as a confirmatory measure. Further investigation of the molecular features of these lesions will, no doubt, contribute significantly to our understanding of their pathogenesis.

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