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Gastrointestinal stromal tumors of the colon and rectum

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A B S T R A C T

Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal tumors of the gastrointestinal tract. GISTs of the colon and rectum are rare, comprising 5% of all cases. There are few data available for colorectal GISTs to guide management. Although they can be small and found incidentally, the majority appear to be at high risk and carry a worse prognosis than gastric GISTs. Surgery remains the mainstay of treatment for primary disease. GISTs are targeted effectively with tyrosine kinase inhibitors (TKIs) such as imatinib mesylate. GISTs are best treated by a multidisciplinary team comprising the surgeon, medical oncologist, pathologist, and radiologist; this approach has the potential benefits of increasing the number of resectable cases through neoadjuvant treatment, optimizing the timing of surgery and organ preservation, reducing recurrence and surgical morbidity, and prolonging survival. On completion of this article, the reader should be able to summarize the diagnosis, specific characteristics, and management of gastrointestinal stromal tumors of the colon and rectum.

Epidemiology

Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal tumors of the gastrointestinal tract. It is estimated that there are 3300–6000 new GIST cases per year in the United States.[1] These estimates represent the minimum incidence, as subclinical GISTs are much more common.[2] They occur most often in the stomach (60%) and the small intestine (30%).[3] Colorectal GISTs constitute 5% of all cases and occur more often in the rectum[4] than the colon.[5] They comprise 0.1% of all colon and rectal tumors.

Pathogenesis

GISTs appear to arise from the interstitial cells of Cajal (ICCs) or their stem cell precursors.[6] ICCs are located in the myenteric plexus of the gut wall and participate in the generation of the pacemaker activity of the gut; they regulate intestinal motility and autonomic nerve function. GISTs likely arise from gain-of-function mutations in the CD117 (c-kit) tyrosine kinase of the ICCs. KIT protein normally regulates cell proliferation and differentiation, cell adhesion, and apoptosis. Gain-of-function mutations lead to uncontrolled cell proliferation and resistance to apoptosis. The discovery of KIT expression and gain-of-function KIT mutations in GIST in 1998 was the basis of the modern concept of GIST—a generally KIT-positive and KIT mutation-driven mesenchymal neoplasm specific to the GI tract. [7]

Approximately 90% of KIT mutations involve exon 11, the juxtamembrane domain. In general, most KIT exon 11 mutants are sensitive to the tyrosine kinase inhibitor imatinib mesylate.[8] Imatinib binds specifically to the kinase domain of these receptors to cause frequently dramatic regression in CD117-positive GISTs. Exon 9 mutants occur predominantly in intestinal GISTs and are less sensitive to imatinib.[8] Secondary KIT mutations (occurring after treatment with TKIs) affect exons 13–17. GISTs with secondary mutations in exon 13 and 14 are sensitive to sunitinib, which is another tyrosine kinase inhibitor.[8] GISTs with no detectable KIT expression have been reported in the range of 17% for the colon and rectum and 9% specifically for the rectum.[9,10]

Platelet-derived growth factor receptor alpha (PDGFRa) mutations can be found in 30% of KIT-negative GISTs. KIT and PDGFRa mutations have been shown to be mutually exclusive in GISTs.[11] PDGFRa mutants are essentially restricted to gastric GISTs, comprising approximately 10% of such cases overall. It was recently discovered that BRAF mutations exist in a subset of patients with wild-type GISTs (KIT and PDGFRa negative)[12]; this has led to the investigation of BRAF inhibitors in the treatment of GISTs.

Mutational status appears to have both prognostic significance and impact on response to TKI therapy. Routine mutational analysis in primary GISTs is not recommended. It should rather be pursued in selected primary cases and in the treatment of metastatic or advanced disease.[13]

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Presentation and diagnosis

Rectal GISTs have been reported between the ages of 17 and 90 years, with a mean age of 59 years. There is a significant male predominance. They may present in any way from small asymptomatic intramural nodules to large masses that bulge into the pelvis and cause pain, rectal bleeding, obstruction, or symptoms of prostatitis.[4]

Colon GISTs have a mean age of presentation of 62 years, with a range of 28–82 years. They have even sex distribution and occur more common in the left or transverse colon (71%). They are typically transmural tumors with frequent intraluminal and outward bulging components. Small colon GISTs can be found incidentally, whereas larger ones present with lower gastrointestinal bleeding, abdominal pain, perforation, obstruction, and an abdominal or pelvic mass.[5]

With regard to imaging, GISTs appear typically as a solid hyperdense-enhancing mass with no surrounding lymphadenopathy on CT and MRI. Large rectal GISTs appear as well-circumscribed, heterogeneous, exophytic masses with areas of hemorrhage or necrosis[14] (Fig. 1). Multiphasic CT imaging techniques are required to recognize the hypervascular hepatic metastases from GISTs, which can be otherwise missed in the routine portal venous phase imaging.[13] Endoscopic ultrasound can demonstrate the origin of the tumor from the muscularis propria and the layers of the wall involved by the tumor.[15,16] Rectal GISTs are FDG avid on PET imaging.[17]

Routine preoperative biopsy of tumors suspected to be GISTs is not necessary if the tumor is easily resectable. These tumors are soft and friable, and there is concern that biopsy may cause tumor rupture or bleeding and lead to tumor dissemination or seeding of the biopsy tract.[18] Conversely, biopsy may be needed if preoperative therapy is being considered for unresectable or marginally resectable tumors.[13] EUS-guided fine-needle aspiration has been reported to be safe and accurate in the diagnosis of GISTs.[19–21]

Histology and immunohistochemistry

Histologically, the majority of colon and rectal GISTs are spindle cell tumors.[4,5] A small percentage has epithelioid morphology. Small GISTs sometimes have extensive calcification, which may reflect their long natural history and tendency to spontaneous regression.

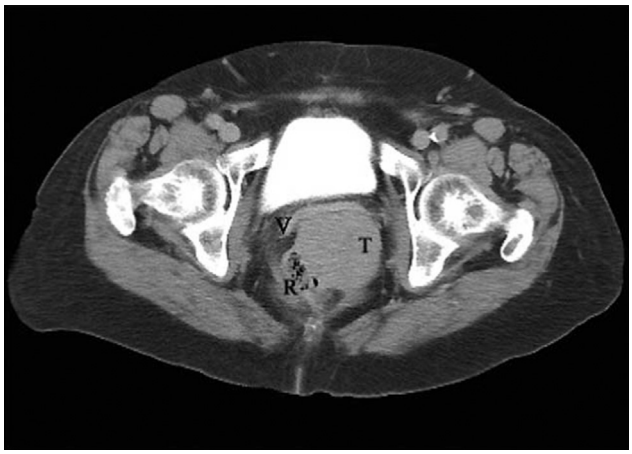

Fig. 1. Computed tomography scan showing a rectal GIST extending from the anterior rectal wall. Notice the bulging of the vaginal wall. V = posterior vaginal wall, R = rectum, T = tumor. (Adapted with permission from Hellan and Maker.[49])

Histologic grading, an important component of soft tissue sarcoma staging, is not well suited to GISTs because most of these tumors have mitotic rates below the thresholds used for grading of soft tissue tumors (the lowest tier of mitotic rates for soft tissue sarcomas is 10 mitoses per 10 HPFs). In GIST staging, the grade is determined entirely by mitotic activity; low-grade tumors have a mitotic rate equal or less than 5 per 50 HPFs, and high-grade tumors have a mitotic rate higher than 5 per 50 HPFs.[22]

CD117, the antigen corresponding to the KIT protein, is the most specific defining marker for GISTs.[23] Approximately 95% of GISTs are positive for KIT (CD117). CD34 is the hematopoietic progenitor cell antigen and another marker commonly seen in GISTs. It has been reported close to 100% in rectal GISTs, but in the range of 50% for small bowel GISTs. Smooth-muscle markers are the smooth-muscle actin (SMA), desmin, and h-caldesmon (HCD). SMA expression has opposite patterns than CD34, being more frequent in the GISTs of small bowel (50%) and rarest in the GISTs of the rectum and esophagus (less than 10%).[24] Desmin and S-100 are seen rarely. Nestin is another marker and has been reported positive in 90–100% of GISTs.[25]

Miettinen et al.[4] studied the clinicopathologic features of 133 anorectal GISTs; 100% were positive for CD117 (this was part of the definition of GISTs), 94% were positive for CD34, 8% were positive for smooth-muscle actin (SMA), and 1% was positive for desmin. The same group reported on 37 colonic GISTs; 76% of cases were CD117 positive, 59% were CD34 positive, 23% were actin positive, and all were desmin negative.[5]

Non-GISTs that are positive for KIT include metastatic melanoma, angiosarcoma, Ewing's sarcoma family of tumors, childhood neuroblastoma, malignant fibrous histiocytoma, extramedullary myeloid tumor, seminoma, Merkel cell carcinoma, and small cell lung carcinoma. These tumors, however, are not driven by pathogenic KIT mutations and are thus not responsive to imatinib treatment.[26] Leiomyomas and leiomyosarcomas of the gastrointestinal tract may often be confused with GISTs. Their well-differentiated smooth-muscle cells are negative for KIT and CD34 and positive for SMA and, usually, for desmin.[27] Schwannomas are distinguished from GISTs by their positivity for S-100 and negativity for smooth-muscle markers and KIT. Solitary fibrous tumors occur in the gastrointestinal tract, mesentery, or retroperitoneum and mimic GISTs histologically. They are typically CD34 positive and negative for KIT and smooth-muscle markers. Desmoid-type fibromatoses (DTFs) may be distinguished from GISTs by their expression of beta-catenin. Inflammatory fibroid polyps are CD34-positive and KIT-negative benign lesions.[24]

GISTs can be confidently diagnosed if the morphology and immunophenotype are concordant; however, any tumors with unusual features should be referred to a center with special expertise.[13]

Table 1
National Institutes of Health consensus criteria for assigning risk to gastrointestinal stromal tumors.

Risk	Size (cm)	Mitotic count (HPF)
Very low	< 2	< 5/50
Low	2–5	< 5/50
Intermediate	< 5	6–10/50
	5–10	< 5/50
High	> 5	> 5/50
	> 10	Any mitotic rate
	Any size	> 10/50

HPF = high-power field.
Adapted with permission from Fletcher et al.[28]