

Gastrointestinal Stromal Tumor of Colon: A Case Report and Review of Literature

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Abstract. *Background:* Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal neoplasm of the gastrointestinal tract. GISTs originate from cells of Cajal and related stem cells. Surgery and imatinib therapy are the main lines of treatment. *Case Report:* We report on a case with GIST in the colon treated with surgical resection followed by adjuvant imatinib therapy. This treatment showed no side-effects, and subsequent colonoscopy was unremarkable. *Conclusion:* The diagnosis was delayed for 12 months after initial presentation of vague abdominal pain, thus highlighting the need to improve clinical suspicion in order to detect GISTs in earlier stages when resection may be curative. Colonic GIST, in particular, may mimic presentation similar to ovarian cyst, as seen in the present case. This case report corroborates that patients with high-grade GISTs can be effectively treated with imatinib therapy. However, decision of treatment may vary depending on the grade of the tumor and side-effects.

The term gastrointestinal stromal tumor (GIST) applies to specific KIT-positive (in 80% of cases) (1) mesenchymal neoplasms of the gastrointestinal (GI) tract. GISTs comprise the majority of GI mesenchymal tumors that originate from intestinal cells of Cajal and related stem cells. Pathogenesis involves KIT signal transduction activation (2-4). Proper identification and definition of GIST have become necessary after the introduction of targeted KIT tyrosine kinase inhibitors such as imatinib [Gleevec (Novartis Pharma)] (5). Data have suggested 3,300 to 6,000 new GIST cases per

year in the United States (1). However, the true incidence of GISTs is unclear since many small tumors may remain undiagnosed (6, 7). The vast majority of GISTs are sporadic, but rare familial cases may be found. GISTs are generally transmural tumors with frequent intra-luminal and outward bulging components. The majority originate in the stomach, while only 1-2% are found in the colon (8). Within the colon, they occur more commonly in the left or transverse colon (71%). Small colonic GISTs may be found with more rarity. Colonic GISTs occur at a mean age of 62 years (range=28-82 years). GI bleeding is the most common clinical presentation of GISTs, but other features may include intestinal obstruction, abdominal pain, perforation, or a palpable pelvic mass, which may be detected incidentally during an endoscopic/radiological procedure or surgery (9, 10).

Prognosis largely depends on the size of tumor and mitotic rate; other prognostic factors are tumor location, tumor resection margins, tumor rupture, and *c-KIT* mutation which may interfere with molecular target therapy efficacy (9). In general, intestinal GISTs are more aggressive than gastric GISTs and they have a high rate of recurrence and therefore worse prognosis (11, 12). Some GISTs are asymptomatic and discovered incidentally and some of them have non-specific symptoms (*i.e.* early satiety, bloating) (13). Contrast enhanced CT is generally the preferred type of imaging for screening and staging. Biopsy is not recommended for a resectable lesions with high suspicion of GIST, however, a biopsy should be considered for a metastatic disease or large lesions (14). Cytological analysis, immunohistochemistry, and reverse transcriptase-polymerase chain reaction (RT-PCR) for *KIT* mutations may permit the preoperative diagnosis of some GISTs by endoscopic ultrasound-guided fine-needle aspiration (15). Tissue, rather than cytological study may be required for a definitive diagnosis. PET scanning is highly sensitive for detecting GIST, but is not specific for making a diagnosis. It is easy to differentiate between the GIST and non-GIST unless the tumor is a GIST that is *KIT*-negative or is a *KIT*-positive

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non-GIST. The identification of tumors as GISTs is based on knowledge of the spectrum of GIST morphology, and can be supported by molecular diagnosis of *KIT* and *PDGFRA* mutations (the latter pertains to gastric tumors). True smooth muscle tumors (rare in the GI tract except in the esophagus and colon) can be distinguished from GISTs by the eosinophilic tinctorial quality of tumor cells, positivity for smooth muscle markers, and negativity for KIT. Desmoids can form large GIST-like masses, but are composed of spindled or stellate-shaped cells in a densely collagenous stroma (16). Negativity for KIT and nuclear positivity for beta-catenin are differentiating features. GI schwannomas, melanoma, and rare primary clear cell sarcoma are S100-positive, usually with characteristic histology. The latter two entities can be KIT-positive. KIT-positive non-GISTs include some sarcomas (especially angiosarcoma and Ewing sarcoma), extramedullary myeloid tumor, seminoma, and a few carcinomas, notably small cell carcinoma of lung. Spurious KIT positivity, seen with some polyclonal KIT antibodies, has been a source of confusion leading to a probable false-positive result for fibroblastic tumors and occasional other sarcomas, such as leiomyosarcomas. Integration of histological features with carefully standardized immunohistochemistry, supported by *KIT* and *PDGFRA* mutation analysis, is the cornerstone of state-of-the art differential diagnosis of GIST. To comprehensively capture all GISTs, KIT immunostaining should be performed on all unclassified epithelioid and mesenchymal tumors of the abdomen (17).

In localized, resectable adult GISTs, if anatomically- and physiologically-feasible, surgery is the primary treatment of choice. Post-surgical adjuvant treatment is recommended (32). Radiotherapy has not, historically, been found effective for GISTs and GISTs do not respond to most chemotherapy medications (18), with responses less than 5% (19). However, three medications have been identified for clinical benefit in GIST: imatinib, sunitinib, and regorafenib. We present a case of GIST that was successfully treated with surgical resection followed by imatinib therapy.

Case Report

A 55-year-old female presented with vague abdominal pain; initial work-up was not revealing. A year later, she had an episode of severe abdominal pain. CT scan revealed a 10-cm pelvic mass of ovarian origin. She underwent right salpingo-oophorectomy with pelvic washings. The tissue obtained was negative for malignant cells. However, a mass in the rectosigmoidal area was noticed. The mass was resected and primary end to end anastomosis of colon was performed. It was 11×9×6.5 cm with an 8.5×7 cm, tan-white, focally-necrotic and hemorrhagic mass. The bowel mucosa was focally infiltrated by the mass. Sectioning of the mass

revealed a heterogeneous yellow-white mass with hemorrhagic areas, as well as focal yellow areas. The mass appeared to abut the resection margin. On microscopy, a spindle cell neoplasm was found, which was 11 cm in maximum dimension, involving the submucosa through subserosa with focal necrosis, and an average mitotic rate of 13/50 HPF. Non-neoplastic colon did not have any significant abnormalities, and proximal, distal and circumferential margins were negative for tumor. Lymph node dissection was negative for tumor.

The diagnosis of a high-grade non-metastatic GIST was made. Pathology showed tumor involving the colonic wall, which belonged to the high-risk category (20). Staining profile for the lesion cells showed that they were positive for c-KIT and CD34, negative for SMA, S-100, ALK, beta-catenin and AE1/3, and equivocal for desmin. The immunohistochemical profile also supported the above diagnosis.

The treatment of patient was initiated with administration of imatinib at 400 mg daily. She underwent oral therapy for 20 months and tolerated the treatment well. At the 16-month follow-up, PET scan showed no abnormalities, and colonoscopy showed no colonic abnormality. At the 20-month follow-up, she remained asymptomatic.

Discussion

A GIST is one of the most common mesenchymal tumors of the GI tract. Mesenchymal tumors constitute only one percent of primary GI cancers (21, 22). The annual incidence of GIST in the United States is at least 4000 to 6000 new cases *i.e.* 7-20 cases per million population (23, 24). More recent data suggest that the frequency of incidentally-detected sub-centimeter GIST lesions may be much higher. Given the relatively low annual incidence of clinical GISTs, only a few microscopic tumors may grow into a clinically relevant size with malignant potential.

The most common location of GISTs is the stomach, accounting for about 60% of all GISTs. Table I indicates how commonly GISTs arise from different sites in the GI tract (25-27).

Imatinib has helped patients with GISTs that are partially resected, although many physicians do not consider imatinib capable of achieving complete cure. Individual patient response to a particular drug will always vary depending on unique circumstances (28). In cases of recurrent GIST, imatinib may slow tumor growth. To date, imatinib therapy has been demonstrated to be effective for up to eighth years without evidence of recurrence (29). However, the efficacy of imatinib varies from case to case and largely depends on the sensitivity of the mutated tyrosine kinase type. Certainly, there is a need to explore other agents where imatinib shows adverse effects or fails to control the disease. The estimation

Table I. Sites of GIST.

Site of origin	Percentage of GIST
Stomach	50-70%
Small intestine	40-45%
Colon, rectum and anus	10-15%
Mesentery and peritoneum	<10%
Esophagus	<5%

of recurrence risk is of paramount importance when selecting patients who would benefit from adjuvant imatinib therapy. However, the selection criteria for patients with high risk of recurrence warranting adjuvant imatinib are not well-established. All GISTs are considered to have malignant potential, and hence, the terms, ‘benign’ and ‘malignant’ are no longer applicable. A degree of risk stratification is possible based upon tumor size, mitotic rate, anatomic site, mutation type, and, in select cases, the presence or absence of tumor rupture. Although these factors have gained acceptance as being predictive of recurrence risk or metastasis (30), it is not clear what cut-offs should be employed to assess disease recurrence and assess patients for imatinib therapy. Thus, each case must be approached individually, with particular attention to the estimated likelihood of disease recurrence with the risk of therapy. In the SSGXVIII trials (Trial SSG XVIII is a Scandinavian Sarcoma Group and Sarcoma Group of the AIO multi-center, prospective, randomized study for evaluation of adjuvant treatment with the tyrosine kinase inhibitor imatinib mesylate of operable gastrointestinal stroma cells tumor (GIST) with a high risk for recurrence), high-risk GISTs were defined as those of size >10 cm with mitotic count >10/50/HPF, >5 cm with a mitotic rate >5/HPF, or a ruptured tumor (31). The present case falls into the high-risk group because of its size and mitotic count. The role of imatinib after surgery in GIST is very important. Data suggest that 36 months of imatinib therapy improves overall and recurrence-free survival of patients with high risk of GIST recurrence (31). The present case also endorses the prescription of three-year adjuvant imatinib therapy after surgery for high-risk patients, since there was no recurrence. Future investigations should be centered on long-term recurrence-free and overall survival, as well as long-term adverse effects of therapy.

Of note, in this case the diagnosis remained elusive for 12 months after initial presentation of vague abdominal pain, thus highlighting the need to improve clinical suspicion in order to detect GIST at earlier stages when resection may be curative. Colonic GIST, in particular, may mimic presentation similar to ovarian cyst, as seen in this case.

There is a need for further studies to clarify the genetic events responsible for the transformation of microscopic GIST lesions into clinically significant ones.

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