Original paper

Gastrointestinal stromal tumors of the colon and rectum

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Gastrointestinal stromal tumors (GISTs) are rare neoplasms, colorectal location being met in less than 5% of cases. Knowledge about this site related particularities are limited.
The aim of this study is to present our experience with colorectal GISTs between 2005 and 2018 from the clinical, morphological, and immunohistochemical perspectives, with emphasis on prognostic factors.
From a total of 203 gastrointestinal stromal tumors registered, 12 were colorectal (6%). The number of colonic tumors surpassed that of the rectum (9 : 3) and on the right side were registered more cases than on the left side (6/3). 9 were primary tumors and 3 were recurrences. Men and women were represented equally and the age range was between 22 and 76. Tumor dimensions varied between 0.5 and 14 cm. Microscopically, spindle cell type was dominant. Mitotic rate was variable between 1 and 115/50HPFs. Accordingly, for primary tumors progression risks were assigned (low risk: 2 cases, intermediate risk: 3 cases and high risk: 4 cases). All GISTs were CD117 and DOG1 positive. Four of the patients died of the disease.

Key words: gastrointestinal stromal tumor, colon, rectum, histopathology, immunohistochemistry.

Introduction

Gastrointestinal stromal tumors (GISTs) are the most common tumors with mesenchymal origin at the level of the digestive tract. Most of the diagnosed GISTs are gastric (60%), followed by those of the small bowel (35 %), less than 5% being colorectal [1, 2]. Regardless of location, the determinant genetic event that initiates tumor development in the majority of cases is a gain of function mutation in the KIT proto-oncogene, resulting in overexpression of KIT protein, a transmembrane tyrosine kinase that promotes cellular proliferation. An accurate diagnosis of gastrointestinal stromal tumor is extremely important due to the therapeutic availability of tyrosine kinase inhibitors such as imatinib, and has become possible with the emergence of specific immunohistochemical markers such as CD 117 (c-KIT) and DOG1 [3, 4].

Colonic gastrointestinal stromal tumors represent 1-2% of all GISTs and are more often reported at the level of the left colon, particularly the sigmoid, affecting older adults with a median age of 60 years [5].

Grossly, they are usually transmural or they can present as bulging, intraluminal or subserosal masses. They proved to have similar histopathological aspects and also a similar immunohistochemical expression with their counterparts from the small bowel. The predominant cell type is spindle, only rarely are epithelioid cells and mixed morphology described. Also, rare lymph node metastases were described, as well as distant metastases (liver, peritoneum) and local recurrences [6]. According to the NIH (National Institutes of Health) risk stratification, which takes into account the tumor size and the mitotic rate, the vast majority of colonic GISTs described to date were high risk accompanied by a significant number of tumor-related deaths [7, 8].

Rectal gastrointestinal stromal tumors are rare, representing 4% of all GISTs [5]. They are often symptomatic, with dimensions varying from microscopic to large, infiltrative masses [9]. Histologically, rectal GISTs have intermediate aspects between those in the stomach and small intestine. Spindle cell morphology prevails, with occasional epithelioid cells [10]. Risk stratification does not accurately apply in rectal GISTs as for other locations, the former having a higher recurrence risk and a great morbidity even at smaller dimensions. Also, the frequency of distant metastases is significantly elevated. In addition, the management of these tumors can be challenging as the pelvis anatomy can impede a proper surgical approach in particular cases, explaining the higher rates of disease progression [11]. Overall, evidence shows that rectal GISTs have a worse prognosis and can be labelled as high-risk tumors in the majority of cases [12, 13, 14, 15, 16, 17].

This paper provides an overview of the clinico-pathologic and immunohistochemical features of colorectal gastrointestinal stromal tumors, aiming to contribute to a better understanding of the particularities of this rare location.

Materials and methods

A retrospective study was performed on all colorectal gastrointestinal stromal tumors diagnosed in our institution between 2005 and 2018. The patients had been previously treated in the Surgery Departments of our institution. The cases were retrieved from the files of the Pathology Department. Demographic data (as sex, age at diagnosis) and clinicopathologic details (as symptoms, type of surgical intervention, tumor location, size and gross findings) were recorded.

Histological slides were reviewed. Between 6 and 17 hematoxylin and eosin (HE) stained sections were analyzed for each case, and particular aspects were noted: as cell type, cellular density, pleomorphism, necrosis, mucosal infiltration, mitotic rate, lymph node status. The diagnosis of GIST was based on HE analysis and confirmed by immunohistochemical tests that were performed on one representative tissue block for each case. CD117 (rabbit polyclonal, ThermoFisher Scientific) and DOG1 (clone SP31, rabbit monoclonal, ThermoFisher Scientific) highly sensitive and specific markers for GIST were tested, and also PDGFRA (Rabbit Polyclonal, ThermoFisher Scientific), CD34 (Clone QBEnd/10, mouse monoclonal, ThermoFisher Scientific), SMA (clone 1A4, mouse monoclonal, ThermoFisher Scientific), Desmin (clone D33, mouse monoclonal, ThermoFisher Scientific), S100 (clone 4C4.9, mouse monoclonal, ThermoFisher Scientific), AE1/AE3 (clone AE1/AE3, mouse monoclonal, ThermoFisher Scientific). Unfortunately, the molecular profile of the tumors could not be evaluated.

A pathologic TNM stage was assigned to each case, determined by tumor size and the presence or absence of lymph node and distant metastases. Risk stratification was performed according to NIH criteria, considering the size and the mitotic rate of the tumor, the risk of disease progression being low, intermediate or high. Also, a prognostic group, ranging from 1 to 6b was assigned to every case, according to Armed Forces Institute of Pathology (AFIP) criteria [18].

The results were presented mostly in a descriptive manner. The limited number of cases made drawing significant statistical conclusions impossible.

This study was carried out according to the principles of the Declaration of Helsinki of good clinical practice. The patients involved in the research signed an informed consent form, allowing the use of their tissues in scientific studies.

Results

A total number of 203 gastrointestinal stromal tumors were registered, 12 being colorectal (6%). 9 were colonic (6 located in the right colon and 3 in the left colon) and 3 were rectal. In 9 cases we evaluated the primary tumor and in 3 cases the pelvic-peritoneal recurrences. At the time of diagnosis, patients had ages between 22 and 76 years: one was less than 30 years old, there were three representatives for each of the 5th, 6th and 7th decade and 2 patients were over 70. An equal number of gender representatives was noted. They presented with symptoms of asthenia, weight loss, abdominal pain, intestinal occlusion. The surgical interventions were hemicolectomy for colonic tumors and rectal amputation for the rectal tumors. The 3 patients with pelvic-peritoneal recurrences had undergone tumor excision.

On gross examination nodular masses were identified, protruding into the lumen and/or on the serosal surface, measuring between 2.8 cm and 14 cm in the case of primary tumors and between 0.5 and

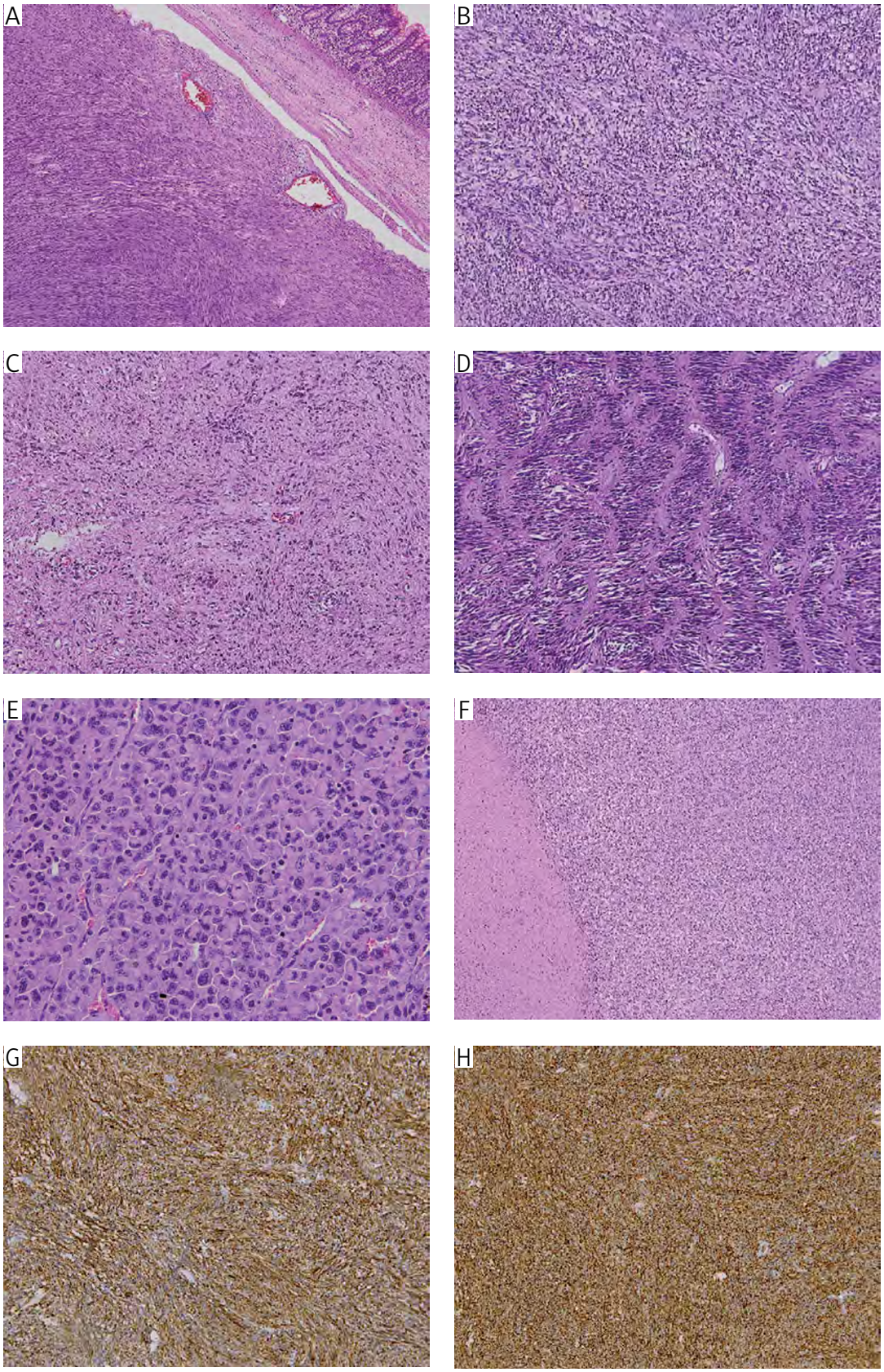

Fig. 1. Histological spectrum and immunohistochemical expression of colorectal gastrointestinal stromal tumors. A) Bulging tumor with evidence of overlying colonic mucosa (HE, magnification 10×). B) Spindle morphology with cytoplasmic vacuolations (HE, magnificatiun 10×). C) Wavy nuclei (HE, magnification 10×). D) Pallisading architecture (HE, magnification 10×). E) Epithelioid pattern (HE, magnification 20×). F) Tumor necrosis (HE, magnification 10×). G) CD117 positivity (magnification 20×). H) DOG 1 positivity (magnification 20×)

Table I. Grading and staging of colorectal gastointestinal stromal tumors

Case no.	Location	Dimensions (cm)	Mitotic rate (50 HPFs)	Risk category (NIH)	Prognostic group (AFIP)	pTNM stage
1	Right colon	6	< 5	Intermediate	3a	II (T3N0M0)
2	Right colon	7.5	> 5	High	6a	IIIB (T3N0M0)
3	Right colon	14	> 5	High	6b	IV (T4N0M1)
4	Left colon	2.8	< 5	Low	2	I (T2N0M0)
5	Rectum	6	< 5	Intermediate	3a	II (T3N0M0)
6	Right colon	4.5	< 5	Low	2	I (T2N0M0)
7	Right colon	5.5	< 5	Intermediate	3a	II (T3N0M0)
8	Left colon	8	> 5	High	6a	IIIB (T3N0M0)
9	Left colon recurrence	9.5	< 5	–	–	–
10	Right colon recurrence	13	> 5	–	–	–
11	Rectum	10	> 5	High	6a	IIIB (T3N0M0)
12	Rectum recurrence	1	< 5	–	–	–

13 cm for recurrences. Two of the primary tumors were less than 5 cm in diameter, and 7 were over 5 cm.

Histologic evaluation revealed a solid proliferation of spindle cells in 9 cases, with fascicular and/or storiform arrangement, and of mixed cell type, epithelioid and spindle, in 3 cases. Nuclear pleomorphism was noted in 4 cases, hypercellularity in 2 cases. Tumor necrosis was identified in one case, and infiltration of muscularis propria and of the mucosa in 3 cases. Other cyto-architectural particularities, i.e. palisading, perinuclear vacuolation, wavy nuclei, were isolated.

Mitoses were counted and reported on 50 HPFs, ranging from 1 to 115. Primary tumors had a mitotic rate less than 5 in 5 cases and more than 5 in 4 cases. Two recurrences had less than 5 mitoses/50 HPFs and one had more than 5 mitoses/50 HPFs. Regional lymph nodes were also evaluated and no lymph node metastases were identified. In one case a distant pulmonary metastasis was reported at the time of diagnosis.

The diagnosis was immunohistochemically confirmed for all tumors. The tests were performed on one representative block from each case, using the antibodies CD117, PDGFRA, DOG1 for positive diagnosis and CD34, SMA, Desmin, S100, AE1/AE3 for differentials. The staining was interpreted only in the presence of positive control. CD117 and DOG1 were positive in all 12 cases, PDGFRA was positive in 5 cases, CD34 in 8 cases, SMA in 4 cases, Desmin in 2 cases and S100 and AE1/AE3 were negative (Fig. 1).

Taking into account tumor size and mitotic rate, a risk group was assigned for every case of primary tumor, according to NIH criteria. Two cases had low risk of disease progression, three cases had intermediate risk and four were high risk. Also, the primary tumors were divided in prognostic groups, according to AFIP criteria (2 cases belonged to group 2, 3 to group 3a, 3 to group 6a and 1 to 6b).

As for pTNM staging, 2 cases were stage I, 3 were stage II, 3 were stage IIIB and 1 was stage IV (Table I).

From the available follow-up data, two cases of high risk primary colonic GIST recurred in the first year from the initial surgical intervention.

Only three patients underwent oncologic treatment with imatinib, two cases with colonic origin that presented with recurrences and one case of high risk rectal tumor. In one case of recurrence the patient did not respond to treatment and died of the disease after less than a year from the diagnosis. The other two cases were still in remission 3 years after the diagnosis.

Four patients died of the disease, all having high-risk colonic tumors, among which three had a recurrence and one was in the metastatic stage, with pulmonary secondary determination. Five cases were disease-free 10 years after the diagnosis, four colonic gastrointestinal stromal tumors and a rectal one, with low and intermediate risk of disease progression.

Discussion

Colorectal gastrointestinal stromal tumors represent a small proportion from the total number of GISTs and extensive studies related to this particular location are few in number, thus proper tumor characterization and data regarding the prognosis are deficient.

The most comprehensive pathologic studies of colorectal GISTs were carried out by Miettinen *et al*., who reported a case series of 44 mesenchymal tumors of the colon, of which 37 were GIST and 7 were leiomyosarcomas. The cases were extracted from the Files of Armed Forces Institute of Pathology

and Haartman Institute of the University of Helsinki, being registered in a 26-years period [6]. From the same data source, Miettinen *et al*. extracted the ano-rectal stromal tumors registered for 28 years, which summed up 133 GISTs, 3 leiomyomas and 8 leiomyosarcomas [10]. Changchien *et al*. reported a series of 46 cases diagnosed as leiomyosarcomas in a medical center in Taiwan over the course of 20 years. After immunohistochemistry was performed, 42 proved to be GISTs [13]. Feng *et al.* used the MEDLINE database and performed a study of 79 cases of colonic GISTs from case reports and clinical studies. The majority of tumors were high risk [7]. Liu *et al*. conducted a population-based analysis on 249 cases of colonic GISTs retrieved from the Surveillance, Epidemiology, and End Results (SEER) database and demonstrated a reduced overall survival compared to other locations [8].

Hassan *et al*. presented a clinical and pathologic study of 18 cases of colorectal GISTs (14 rectal and 4 colonic) registered in a 25-years period at Mayo Clinic, USA. The cases were associated with a poor prognosis [19]. By contrast, Liu *et al*. found that ano-rectal GISTs have a better outcome, compared to GISTs in other locations, in part because they are diagnosed at an earlier stage [20].

We managed to gather a total of 12 cases of colorectal GISTs diagnosed in our institution during the course of 14 years. Although the number of cases is limited, it reflects the low incidence of these tumors and is rather close to the experience of other health care centers. The patients diagnosed with gastrointestinal stromal tumors were over 50 year old in most of the cases, as Sert *et al*. also observe in their study [21]. Regarding site-related particularities, evidence shows that GISTs with different locations along the gastrointestinal tract have various clinical, histological and genetic features. The presentation symptoms of the patients with colorectal GISTs include the following: abdominal pain, obstruction, bleeding, perforation and abdominal or pelvic mass [7, 22]. Rectal GISTs can be incidentally detected on prostatic biopsy fragments or hemorrhoidopexy specimens [23, 24, 25]. Regarding the dimensions, few studies conducted on a significant number of cases showed that colonic GISTs were large tumors when they were clinically detected. Also, microscopic, incidental tumors of this type were discovered in surgical colon resections performed for different causes [26]. Rectal tumors have variable dimensions with an evolving spectrum from indolent to highly aggressive. Neoadjuvant therapy with imatinib proved to be useful in sphincter preservation in cases with indication for pelvic exenteration or abdomino-perineal resection, leading to tumor shrinkage and lowering the mitotic rate. Cavnar *et al*. stated that imatinib therapy prior to surgery is associated with improved oncologic outcome in cases of high-grade rectal GISTs, due to higher rates of organ and sphincter preservation and lower rates of positive margins [27].

Zhu *et al*. conducted a comparative study of different GIST locations and proved that overall survival is superior for rectal location compared with colonic and even gastric origin of the tumor. This is due to the fact that a higher percentage of rectal GISTs received systemic therapy when compared to the other locations [28].

Although microscopically, colonic GISTs are similar to those of the small intestine, and rectal ones have aspects intermediate between the gastric and small bowel counterparts, clinical evolution seems to be less favorable, due to frequently larger tumors at diagnosis [29]. Our case series sustains this observation, the dominant cellularity being of spindle type and only 2 tumors measuring less than 5 cm at diagnosis. Consequently the risk of disease progression is higher and the mortality is also higher. Accordingly, we registered 5 recurrences and 4 deaths from the total of 12 cases. No predilection for a specific gender or age range was observed.

The available data so far suggest that the frequency of rectal GISTs exceeds that of colonic GISTs, but in our experience rectal location is far less common (rectum : colon = 3 : 9). Also, left colon, particularly the sigmoid, is known to be more often involved than the right colon. In our study, the ratio is reversed (left : right = 3 : 6). There were no significant clinico-pathologic differences between colonic and rectal GISTs. The 3 rectal GISTs were present in both genders, at different ages, had spindle and mixed cellularity, were of intermediate risk or high risk, with one recurrence, but no mortality was registered, in contrast to colonic GISTs.

The majority of soft tissue tumors of colon and rectum were previously considered to be leiomyosarcomas. Later on, with the development of molecular biology and immunohistochemistry, specific entities could be diagnosed (gastrointestinal stromal tumors, leiomyomas, leiomyosarcomas, schwannomas, *etc*.). As stated by Sert *et al*., a GIST diagnosis should be immunohistochemically confirmed, CD117 and DOG1 being positive in up to 95% of cases [21]. Less sensitive and specific, CD34 is also expressed in these tumors, other markers positive in a significant number of cases being represented by PDGFRA (a tyrosine kinase mutually exclusive with CD117), H-caldesmon, SMA, S100 or Desmin [30, 31, 32, 33]. The immunophenotype of the tumors we have studied presented no particularities, being in accordance with the published data.

Although facing limitations determined by the retrospective nature of our study that was extended on a period of 14 years, accompanied, inherently by a loss of data and because of the limited number

of cases due to the rarity of these tumors, we hereby presented the experience of our center in colorectal gastrointestinal stromal tumors with the intent to contribute to a more accurate description and understanding of this tumor category.

In conclusion, colorectal location of gastrointestinal stromal tumors is a rare instance representing 6% of the total number of GISTs. In contrast to the existing data, the colon was more frequently involved than the rectum, and the right colon more than the left colon. The majority have a high risk of disease progression. Further, more extensive studies are needed to improve the characterization and management of colorectal gastrointestinal stromal tumors and also to elucidate the prognostic significance of this particular location.

The authors declare no conflict of interest.

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