

## Original Article

# Superficial leiomyomas of the gastrointestinal tract with interstitial cells of Cajal

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**Abstract:** Objective: Some authors suggest common origin of gastrointestinal stromal tumors from stem cells, which may show diverse differentiation. There are reports in which cells morphologically identical to the interstitial cells of Cajal are found in deep leiomyomas. The aim of this study was to demonstrate CD117 positive cells in superficial gastrointestinal (GI) leiomyomas and to find other cells that would suggest diverse differentiation in histologically typical leiomyoma. Materials and methods: We analyzed 8 cases of superficial leiomyomas and one deep leiomyoma, received in our institutions as endoscopically or surgically obtained material. The tumor sections were immunohistochemically stained with CD117, CD34, NF, S100,  $\alpha$ SMA, desmin, caldesmon and mast cell antigen. Results: All leiomyomas showed diffuse positivity for  $\alpha$ SMA, caldesmon and desmin. All of them had CD117 and CD34 positive cells morphologically identical to the interstitial cells of Cajal between smooth muscle fibers, 5 had S-100 and NF positive cells and 2 showed positivity for GFAP. The cells were found in different quantity; they were usually diffusely scattered through the tumors without predilection site, forming small groups in some areas. Conclusion: CD117, CD34, S-100 and NF positive cells are present in superficial leiomyomas and they may suggest common origin of GI stromal tumors.

**Keywords:** Leiomyoma, Cajal cells, CD117, CD34, gastrointestinal tract

## Introduction

Gastrointestinal stromal tumors (GIST) are the most frequent mesenchymal tumors of the gastrointestinal tract (GI) [1]. They are rare neoplasms arising from interstitial cells of Cajal (ICC) and their precursors of the GI, and represent about 0.1-1.0% of all neoplasms of the GI [2, 3]. GISTs constitute approximately 5% of all the sarcomas with incidence of 1-2 cases/100000 habitants [1]. Most of the GISTs arise in the stomach and small intestine, but other sites such as the esophagus, colon, and rectum are also involved [4-7].

In pre-KIT era GISTs were considered as tumors arising in smooth muscle of the GI but nowadays GIST are considered as tumors of the gastrointestinal mesenchyme which express the tyrosin kinase KIT receptor, presenting in high

percentage thereof mutations in the proto oncogene c-kit [1]. Therefore GISTs are distinguished from other mesenchymal tumors by their unique expression of c-kit protein (CD117). The majority of GISTs are usually positive for CD117 in about 95% of cases, CD34 in about 70% of cases, smooth muscle actin in approximately 30%-40% of cases, S-100 in near 5% of cases, and desmin in approximately 2% of cases [8].

True leiomyomas are rare tumors that can be found anywhere along the gastrointestinal tract, more commonly in the esophagus, stomach and colon [9, 10]. They arise in muscularis mucosae or muscularis propria of the GI and based on their origin from muscularis mucosae or muscularis propria they can be classified as superficial or deep leiomyomas. Opposite to GIST they are CD117 and CD34 negative and  $\alpha$ SMA and desmin positive tumors [9, 11].

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Although leiomyomas arise in muscle layers of the GI there are reports in which authors have demonstrated the presence of CD117 positive cells, morphologically identical to the interstitial cells of Cajal in these tumors [12, 13].

We were intrigued whether the superficial leiomyomas may contain CD117 positive cells, what kind of distribution they show and is it possible to find other cells that would suggest divergent differentiation in histologically typical GI leiomyoma.

### Material and methods

We analyzed clinical, radiological and pathological findings of 9 patients with leiomyomas out of 38 patients with gastrointestinal stromal tumors whose endoscopically or surgically obtained material was received for histopathological analysis at the Institute of Pathology, Faculty of Medicine in Skopje for the period of 2 years.

The histological analysis was performed on 17 gastric GISTs, 9 small intestine GISTs, one retroperitoneal, one mesenteric and one GIST diagnosed as liver metastasis found in 20 male and 9 female patients with mean age of 59 years. There was one GANT, one schwannoma, one leiomyosarcoma and 9 leiomyomas.

For the purpose of this study we focused on the leiomyoma group and we made a retrospective analysis of the clinical and radiological patients' data using the archive files from the University Clinic of Gastroenterohepatology and the University Clinic of Abdominal Surgery in Skopje. We also used the archive material from the Institute of Pathology, using pathological reports, paraffin blocks and histological slides.

For the leiomyoma group new sections of the paraffin blocks were made and additional immunostainings with antibodies against Caldesmon (Dako/Clone QBEnd-10/Code M7165, dilution 1:50), S-100 protein (Dako/Code Z 0311, dilution 1:400), NF (Neuron Fiment, Dako /Clone 2F11/Code M0762, dilution 1:100), GFAP (Glial Fibrillary Acid Protein, Dako/Clone 6F2/Code M 0761, dilution 1:600) and MCA (Mast Cell Tryptase antigen, Dako/Clone AA1/Code M7052, dilution 1:100) were performed using Avidin-Biotin Immunoperoxidase Complex technique. For the visualisation of the

antigen-antibody reaction, LSAB and En-Vision kits from DAKO were used.

Immunostainings with  $\alpha$ SMA (Dako/Clone 1A4/Code M0851, dilution 1:100), Desmin (Dako/Clone D33/Code M0760, dilution 1:50), CD117 (Dako/Code A4502, dilution 1:400) and CD34 (Dako/Clone QBEnd-10/Code M7165, dilution 1:50) were already performed during the diagnosing process.

Three pathologists reviewed the slides separately in order to obtain objective findings of the presence of CD117 positive cells, morphologically identical to the interstitial cells of Cajal and their distribution through the tumor. They also analyzed the other above mentioned immunohistochemical staining.

The immunostained cells were semi-quantitatively analyzed and the results were classified as -, +, ++ and +++, as following:

-, No immunostained cells were found; +, < 10 immunostained cells per 400 nuclei/HPF; ++, < 50 immunostained cells per 400 nuclei/HPF; +++, > 50 immunostained cells per 400 nuclei/HPF; 100%, all or almost all of the cells showed positive signal.

### Results

All leiomyomas were diagnosed as GI polyps at endoscopy. On endoscopic ultrasound all leiomyomas were hypoechoic lesions originating from the muscularis mucosa.

There were 6 colonic, 2 rectal and one esophageal leiomyomas. All tumors were asymptomatic, except one which caused bleeding. One patient who had an associated gastric cancer had symptoms characteristic for gastric cancer. The associated leiomyoma was an incidental finding. Demographic and clinical data of the analyzed cases are listed in **Table 1**.

### Histology

All analyzed leiomyomas were well-circumscribed tumors composed of well-differentiated smooth muscle cells. They contained short fascicles of spindle-shaped smooth muscle cells with abundant cytoplasm and oval, pale nuclei without any atypia. Mitotic activity was absent.

All colonic/rectal leiomyomas were superficial, originating from muscularis mucosae and were

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**Table 1.** Demographic and clinical data of leiomyomas

Case	Gender	Years	Localization	Symptoms	Dimensions	Endoscopic Dg
1	m	68	Rectum	asymptomatic	0.7×0.6×0.4	Polyp
2	f	60	Sigmoid colon	asymptomatic	0.6×0.6×0.3	Polyp
3	m	54	Rectum	asymptomatic	0.5×0.5×0.3	Polyp
4	m	70	Colon	asymptomatic	0.5×0.4×0.3	Polyp
5.	f	57	Sigmoid colon	asymptomatic	0.5×0.4×0.3	Polyp
6.	m	52	Descending colon	bleeding	2×0.8×3	Polyp
7	f	73	Sigmoid colon	asymptomatic	0.5×0.3×0.2	Polyp
8	m	69	Colon associated with 2 colonic adenomas	asymptomatic	0.7×0.6×0.4	Polyp
9	f	72	Esophagus with associated advanced gastric Ca	Incidentally identified	1.2 diameter	Polyp
Total 9	5 male 4 female	Mean 63.8 Min 52, Max 73	Rectum 2 Colon 6 Esophagus 1		Min 0.5 cm Max 1.2 cm	

**Table 2.** Immunohistochemical results and quantitative analysis of cells in GI leiomyomas

Case	SMA	Des	Caldes	CD117	CD34	S-100	MCA	NF	GFAP
1	100%	100%	100%	++	+	-	-	-	-
2	100%	100%	100%	+	+	+	-	-	-
3	100%	100%	100%	++	++	-	-	+	100%
4	100%	100%	100%	+	+	+	-	+	100%
5	100%	100%	100%	+++	+	+	-	+	-
6	100%	100%	100%	+	+	+	+	-	-
7	100%	100%	100%	+	+	-	-	+	-
8	100%	100%	100%	++	+++	+	+	+	-
9*	100%	100%	100%	+++	+++	-	++	-	-

\*Esophageal leiomyoma.

covered by normal mucosa. The esophageal leiomyoma was mainly localized in muscularis propria containing a part with a close contact with muscularis mucosa. The deeper sections did not change the histological features, so we considered this tumor as a deep one originating from muscularis propria due to the main mass present in the muscularis propria.

### Immunohistochemistry

The results from the immunostainings are shown in **Table 2**.

All leiomyomas showed diffuse and strong positivity for αSMA, desmin and caldesmon (**Figure 1A, 1B**).

All of them showed presence of morphologically identical to the interstitial cells of Cajal, CD117 positive cells between smooth muscle

cells. The cells were spindle-shaped with elongated nuclei, and some of them had clearly visible cytoplasmic processes that project secondary branching processes (**Figure 2A-D**). Most of them were orientated along the long axis of surrounding smooth muscle cells.

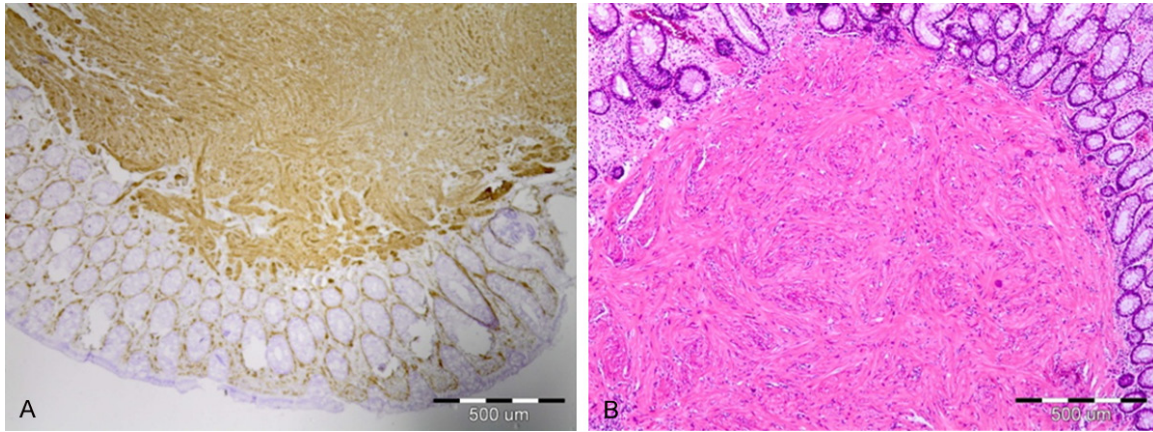
They were diffusely scattered through the tumors without predilection site. They were visible in the periphery of the tumors as well as in the central portions of them. Some cells had perivascular arrangement and some of them were grouped in small clusters.

Majority of these CD117 positive cells were CD34 positive in all cases. CD34 positive cells showed the same morphology, although we have noticed that some CD34 positive cells had lost their orientation along the long axis of surrounding smooth muscle cells (**Figure 3A**).

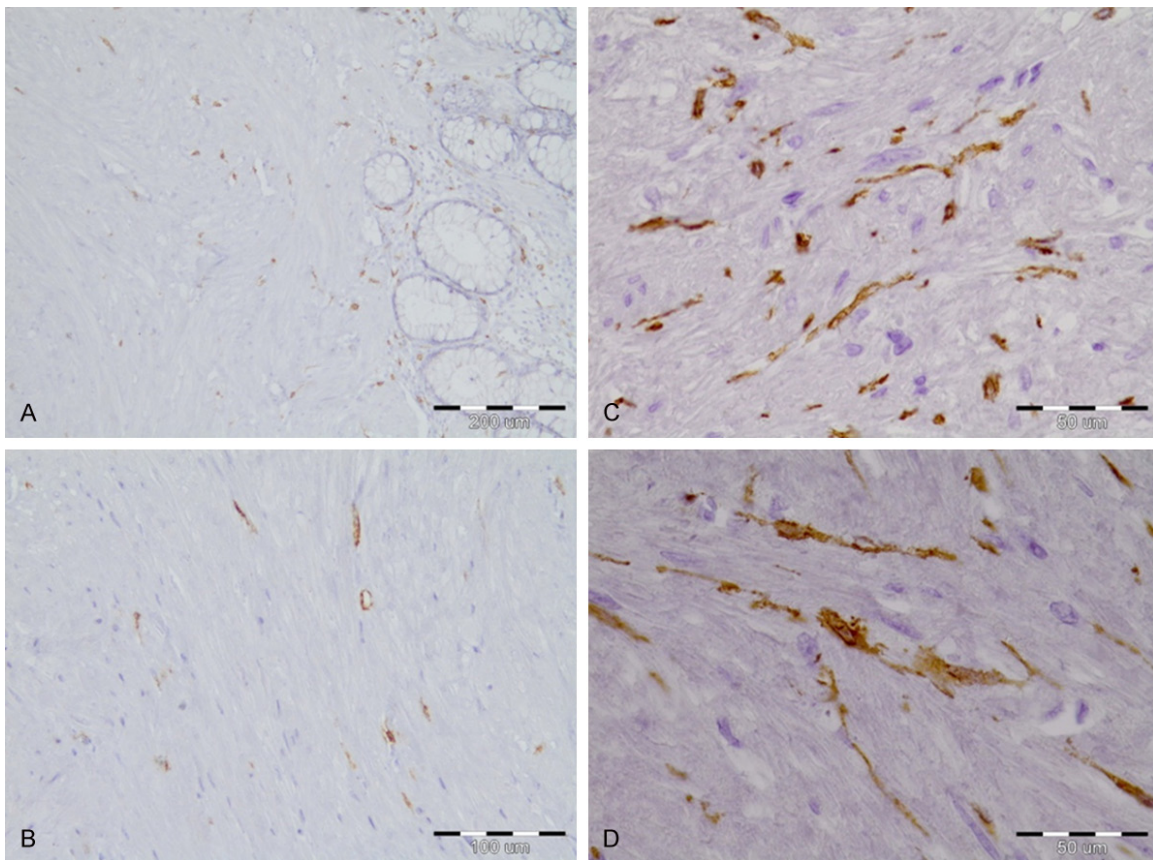
There were S-100 positive cells in 5 cases. They were rare cells, spindle-shaped; some of them plump. We found these cells to have similar but not identical morphological features as those that were stained with CD117 (**Figure 3B**).

NF positive cells were found in 5 cases. These cells were quantitatively less common compared to the CD117 positive cells in all cases.

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**Figure 1.** A. Superficial colonic leiomyoma showing diffuse SMA positivity (Immunostaining SMA  $\times 40$ ). B. Superficial colonic leiomyoma covered by regular mucosa (HE  $\times 40$ ).

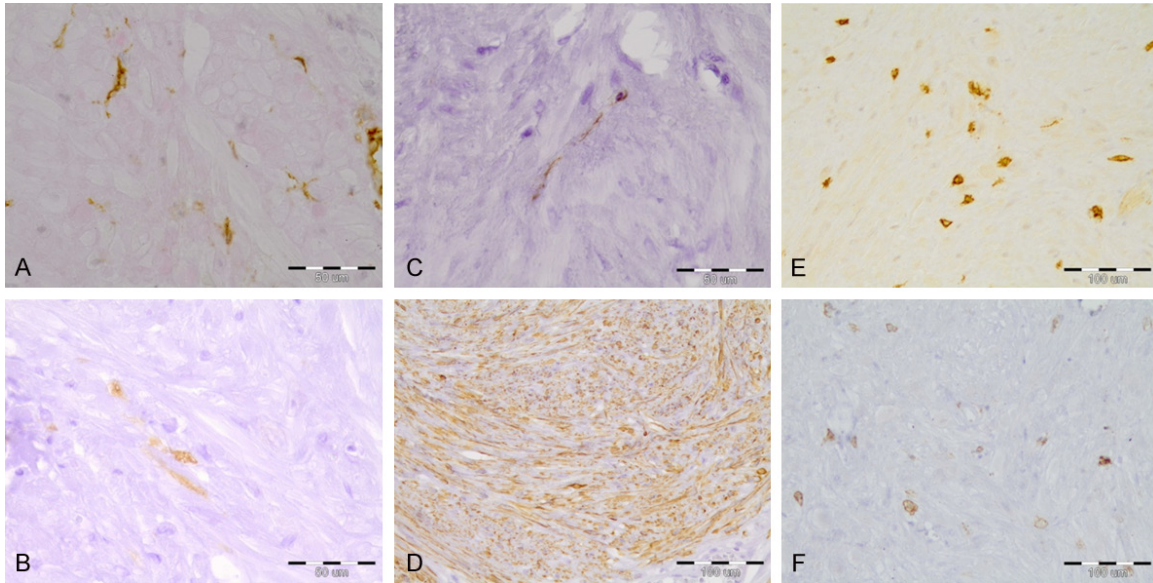


**Figure 2.** A. Colonic leiomyoma showing presence of CD117+ cells between the tumor smooth muscle cells also present in mucous lamina propria (Immunostaining CD177  $\times 100$ ). B. Spindle shaped CD117+ cells in colonic leiomyoma, orientated along the long axis of surrounding smooth muscle cells (Immunostaining CD177  $\times 200$ ). C. A group of Cd117+ cells morphologically identical to the interstitial cells of Cajal in the esophageal leiomyoma (Immunostaining CD177  $\times 400$ ). D. CD177+ cells with clearly visible cytoplasmic processes with secondary branching, in colonic leiomyoma (Immunostaining CD177  $\times 400$ ).

The cells showed somewhat different morphology. Some of them were elongated and some

were more oval to round. Their nuclei were smaller than the nuclei of the CD117 positive

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**Figure 3.** A. CD34 positive cells with the same morphology in colonic leiomyoma. Some of them had lost their orientation along the long axis of surrounding smooth muscle cells (Immunostaining CD34  $\times 400$ ). B. S-100 positive cells in superficial colonic leiomyoma (Immunostaining S-100  $\times 400$ ). C. NF positive cells in superficial colonic leiomyoma (Immunostaining NF  $\times 400$ ). D. GFAP positivity in almost all smooth muscle cells in superficial colonic leiomyoma (Immunostaining S-100  $\times 200$ ). E. MCA positive plump spindle, round to oval shaped cells (Immunostaining MCA  $\times 200$ ). F. CD117 positive plump cells with the same morphology of MAC positive cells (CD117+ mast cells).

cells. In general, these were rare cells scattered through the whole tumor (**Figure 3C**).

GFAP staining was diffusely positive in approximately 100% of cells in 2 cases and negative in 7 cases of leiomyomas (**Figure 3D**).

MCA positive staining was found in 3 cases. The MAC positive cells were plump spindle, round- to oval-shaped cells and had more round nucleus than CD117 positive cells. The positive stain was seen in the cytoplasm of the cells. Some of them showed stellate branching of the cytoplasm. The cytoplasmic processes were shorter than those seen in the CD117 positive cells. Mast cells differed from the cells which showed CD117 positivity not only by their morphology and positivity for MCA but also by their position in consequent serial sections different than the position of the CD117 positive cells (**Figure 3E, 3F**).

### Therapy

Patient with esophageal leiomyoma (incidentally found) and associated gastric cancer underwent total gastrectomy and chemotherapy.

Eight leiomyomas were enucleated endoscopically and all of the patients were followed up for 12 months. There were no reports for recurrence or new GISTs.

### Discussion

Stromal tumors of the GI are primary non-epithelial neoplasms that can affect the whole GI (esophagus, stomach, small and large bowel, appendix) including omentum, mesentery and retroperitoneum. According to Juan Rosai [11] they can be roughly divided in 4 main categories:

- 1) Tumors showing differentiation toward smooth muscle cells, expressing immunohistochemically smooth muscle actin, desmin, calponin, heavy caldesmin, and/or myosin.
- 2) Tumors showing differentiation toward neural type elements expressing immunohistochemically neural/endocrine markers chromogranin, synaptophysin, neurofilaments, Leu-7, neuron-specific enolase (NSE), glial fibrillary acid protein (GFAP), and S-100 protein. These tumors compose the GANT (gastrointestinal autonomic nerve tumors) group.
- 3) Tumors showing dual differentiation toward smooth muscle and neural-like elements.
- 4) Tumors lacking differentia-

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tion toward either cell type named GISTs (gastrointestinal stromal tumor) showing in about 95% of adult somatic mutation of CD117 (c-kit), which is usually absent in GISTs of children.

It is considered that GISTs are neoplasms arising from interstitial cells of Cajal [2, 3].

Microscopically, most of the GISTs consist of spindle-shaped cells (70%), but some GISTs consist of rounded cells (epithelioid type, 20%) or a mixture, but they can also be pleomorphic. They generally express vimentin, CD117, CD34 and DOG1 immunohistochemically [13]. According to the consensus report of GIST by Fletcher et al. [19, 20], the malignant potential of GIST depends on tumor size and mitotic counts. In very low malignant risk group, tumor size is less than 2 cm and mitotic counts are less than 5 per 50 high power fields (HPFs). In low malignant risk group, tumor size is 2 cm < 5 cm, and mitotic counts are < 5/50 HPFs. In intermediate risk group, tumor size is 5 cm < 10 cm, and mitotic counts are < 5/50 HPFs. In high risk group, tumor size is > 10 cm, and mitotic counts are > 10/50 HPFs [12, 13].

Gastrointestinal leiomyomas are tumors arising from smooth muscle cells of muscularis mucosae, muscularis propria, or vessel-related smooth muscle cells. Microscopically these tumors are composed of spindle-shaped cells, similar to those of some GISTs, and can appear quite uniform in GIST as in leiomyoma. Immunohistochemical analysis is a helpful tool for diagnosis of stromal gastrointestinal tumors. The accurate diagnosis is important because the prognosis and therapy of the patients with gastrointestinal stromal tumors depend on it.

The overlapping histological features of GIST and leiomyoma may become a diagnostic problem for the pathologist, especially in fine needle and core biopsy specimens and especially after few reports of interstitial cells of Cajal or cells similar to them being found in some gastrointestinal leiomyomas [14-17].

Interstitial cells of Cajal are mesenchymal cells, recognized as peacemaker cells for gastrointestinal movement and are suggested to be mediators of neuromuscular transmission [18]. There are several types of ICC located in the musculature of the GI with specific distribution,

arrangement and cell shape, depending on their location in the tissue of GI. According to their localization in the GI they can be divided in ICC of the circular muscle (ICC-CM), ICC of the longitudinal muscle (ICC-LM), ICC of the myenteric plexus (ICC-MP or ICC-AP/Aurbach's plexus), ICC of the deep muscular plexus (ICC-DMP), ICC of the submucosa and submucosal plexus (ICC-SM and ICC-SMP) and ICC of subserosa (ICC-SS)-the last found in small and large intestine of mice.

They make two- and three-dimensional networks and relationships to local nerve plexuses and smooth muscle cell [18-20].

All subtypes of ICC share common ultrastructural features, but some of them depending on their species and anatomical location show morphological heterogeneity ranging from features similar to fibroblasts to those specific and typical to smooth muscle cells.

Morphologically they are similar in size to the adjacent smooth muscle cells or may be smaller. They may be spindle-shaped or stellate having secondary and tertiary branching. These located between smooth muscle cells are spindle-shaped with few long cell processes and lay parallel to the axis of the muscle bundles [19, 20].

ICC depends on stem cell factor (SCF) for their development and expresses the protooncogene c-kit which encodes a receptor tyrosine kinase (KIT). Nowadays antibodies against KIT like CD117 are the main markers for visualization of ICC [21, 22].

Some authors support the concept that ICC share precursors with smooth muscle cells. Wide range of phenotypes of ICC may suggest that mesenchymal progenitor cells in a circumstance of blockade of Kit signaling may differentiate to smooth muscle cell phenotype [11, 15, 19].

Deshpande et al. [15] reported a finding of CD117 positive cells, morphologically identical to the interstitial cells of Cajal in deep GI leiomyomas and their entire absence in superficial esophageal and colonic/rectal leiomyomas.

There are few other reports about the same issue [16, 17] that have intrigued us, together

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with the above-mentioned concepts of divergent differentiation in stromal GI tumors, to analyze the superficial colonic leiomyomas in order to find a base for the concept of common progenitor cell in stromal GI tumors.

We found CD117 positive cells in all analyzed tumors. Quantitatively they were more present in the deep esophageal leiomyoma, but they were also present in all superficial colonic/rectal tumors, less common, and haphazardly, diffusely spread through the whole tumor. CD117+ mast cells are reported to be present in gastrointestinal leiomyomas [16]. We identified mast cells by immunostaining against mast cell antigen (in 2 tumors) and hence we differentiated CD117+ mast cell from the other CD117 positive cells. We also found NF positive and S-100 positive cells. We also found positivity for GFAP in 2 tumors in about 100% of the cells.

Distinctive patterns of immunohistochemical expression of various antibodies are described in GISTs. True leiomyomas are reported to be positive for vimentin, SMA, desmin, and caldesmon; some have shown weak reactivity for S-100 and weak cytoplasmic positivity for GFAP [23-27].

These reports and our results obtained in a small series raise more questions for future larger studies in which a common progenitor or maybe a stem cell should be confirmed in gastrointestinal leiomyomas. In addition, other studies have to clarify the development of cells and their differentiation as well as the factors influencing them.

Colonization and hyperplasia of non-neoplastic ICC cells might result in presence of CD177+ cells in GI leiomyomas but it seems quite acceptable to hypothesize that stromal tumors derive from a common stromal cell which differentiate in several lines with the predominant differentiation in smooth muscle cells in gastrointestinal leiomyomas. The finding of CD117 positive cells morphologically identical to the ICC in superficial and not only in deep leiomyomas and the finding of NF+ and S-100+ cells and GFAP+ cells support the idea of common progenitor cell in GI stromal tumors and its divergent differentiation.

### Disclosure of conflict of interest

None.

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