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ARTICLE

Gastrointestinal Stromal Tumors: A Clinicopathologic and Immunohistochemical Study of 136 Cases

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The clinicopathologic features of 136 gastrointestinal stromal tumors were analyzed. The tumors occurred in 60 women and 76 men, ranging in age from 19 to 88 years (median 59 years, mean 59.2 years). Sixty-one cases arose from stomach, 38 from small intestine and 11 from colon or rectum. Abdominal cavity was indicated as tumor site in 10 cases, but the extragastrointestinal origin using strict criteria was not proved. Four locally recurrent cases and 12 metastatic samples were also included. The primary and recurrent tumors ranged in size from 0.5 to 30 cm (mean 8.3 cm). The large number of high-grade cases (85 of 112 classifiable) is alarming and emphasize the importance of oncology care. Histologically, ninety-two cases were classified as spindle cell while 11 as epithelioid GIST. Mixed cellularity was seen in 33 cases. Skeinoid fibers were present in 14 and coagulation necrosis in 40 primary cases. Ulceration observed by microscopic examination was common (36 of 110 cases, 32.7%), explaining the clinically frequently observed gastrointestinal bleeding. Unusual histological features such as stromal hyalinization and nuclear palisading were present in 30 and 27 cases, respectively. Immunohistochemical CD117 (c-kit) positivity was documented in 133 cases. Three cases with CD117 negative results were included, because their morphology was most consistent with GIST and immunohistochemical reactions excluded the possibility of other neoplasms. CD34 positivity was seen in 70%, alpha-smooth muscle actin positivity in 39.6% of examined cases. Only one case showed desmin reactivity and seven had S100 positive tumor cells. For h-caldesmon 39 cases proved to be positive (60.9% of the tested cases). (Pathology Oncology Research Vol 11, No 1, 11–21)

Key words: c-kit; CD117; gastrointestinal stromal tumor (GIST); inflammatory fibroid polyp; leiomyoma; leiomyosarcoma; schwannoma

Introduction

Gastrointestinal stromal tumor (GIST) is a rare but important type of tumors arising within the gastrointestinal tract. In the past few years revolutionary changes in our knowledge about GIST resulted in much attention to different topics related to it. Cornerstones of this course were the observation of activating c-kit mutation in GIST by Hirota et colleagues,[12] and postulation by Kindblom and collegues[15] that GISTs differentiate toward interstitial cells of Cajal. The next fundamental result was the effective use of tyrosine kinase inhibitor STI571 (imatinib mesylate, Glivec®) in a patient with metastatic gastrointestinal stromal tumor, published by Joensuu and colleagues[14] in 2001. Treatment of GIST with imatinib is a part of a process that caused paradigm shift in oncology, in association with the introduction of the so-called targeted therapies.

In the last years several articles focusing on GIST have been published. A large number of these discussed pathology, molecular pathomechanism and clinical relations of GISTs, but in contrast to the huge number of publications, which are mainly case reports and reviews,[2,5,10,23] relative-

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ly limited number of reports on large clinicopathological series can be find.[4,7,9,11,21,22,25,29,34,35] Reports focusing on gastrointestinal stromal tumors, published before the use of CD34 and CD117 immunohistochemistry, should be read with skepticism because of the considerable phenotypic and immunohistochemical overlapping between GISTs and leiomyogenic neoplasms. In daily pathological diagnostic work, however, differential diagnostic problems exist, and in many cases it is not easy to predict the biologic behavior of GISTs.

The purpose of this prospective study was to analyze the clinicopathologic features in a large series of GISTs, and to discuss problems with everyday pathological diagnostic work, excisional, endoscopic and core biopsy samples, and immunoreactivity of GISTs.

Materials and methods

Case material and follow-up

At the end of 2000 a prospective, non-randomized study was launched in Hungary to treat 30 patients with gastrointestinal stromal tumor. The condition of the treatment with imatinib mesylate was reviewing the pathological samples and determination of c-kit reactivity. Since the closing of the study,[6] the pathologists throughout the country have considered the possibility of GIST much better than before,[30] and have sent several cases to the centers. The consultations were initiated partly by clinicians with the intention to determine c-kit status in the hope that a large abdominal mass or an advanced disease will be proved c-kit positive GIST. The cases were referred from different parts of the country, and among surgical resection specimens included 4 excisional, 7 endoscopic and 10 core biopsy samples.

Clinical and follow-up information were obtained from the referring pathologists, histological requisition forms and medical records.

From the beginning of 2001 until November 2004 we collected 136 GIST cases. All cases from consultation files of the authors and from the files of National Institute of Oncology were included and no exclusion from a specific point of view was made.

The diagnosis of GIST was made in those cases in which mesenchymal tumors of the gastrointestinal tract had the histologic features defined by a consensus in 2002[8] and were positive for CD117 (c-kit). Three cases with CD117 negative results were included, because their morphology was most consistent with GIST and immunohistochemical reactions excluded the possibility of other neoplasms.

Histological evaluation

Tumors were evaluated for size, involvement of the different layers of the tubular organs of gastrointestinal tract, cell type (spindle vs. epithelioid), specific histological patterns, skeinoid fibers, coagulation necrosis (with ghosts of tumor cells), calcification, vascular pattern within the tumor, stromal or perivascular hyalinization, the presence of myxoid stroma, border of tumors, and mitotic activity. Mitoses were counted on 50 consecutive HPFs in the most cellular areas (area of an individual field: 0.2 mm^2).

To estimate the metastatic risk of GIST we used the scheme of the NIH consensus approach (based on tumor size and mitotic count), which describes the tumors as high-risk (HR), intermediate risk (IR), low-risk (LR), and very low-risk (VLR).[8]

Table 1. **Immunohistochemical antibody specifications**

Antibody	*Clone*	*Dilution*	*Source*
CD117 (c-kit)	Polyclonal (A4502)	1:100	DAKO
CD34	QBEND10	1:50	DAKO
α-smooth muscle actin	1A4	1:50	DAKO
Desmin	D33	1:50	DAKO
S100 protein	Polyclonal	1:2000	DAKO
h-Caldesmon	Ab-1	1:50	Neomarkers
Vimentin	V9	1:70	DAKO
Cytokeratin	AE1/AE3	1:50	DAKO

Immunohistochemistry

Antibodies to the following antigens were used: c-kit (CD117), CD34, α-smooth muscle actin, desmin, h-caldesmon and S100 protein. In selected cases vimentin and cytokeratin reactions were also performed. The primary antibodies, their dilutions, and commercial sources are listed in *Table 1*. The staining for CD34, c-kit, α-smooth muscle actin and S100 protein was interpreted only when positive normal cells were present (endothelial cells, mast cells, or Cajal cells, vascular pericytes, dendritic cells or nerves, respectively). Immunostains were interpreted as positive when more than 5% of the cells demonstrated staining.

The positive reactions were estimated as percentage of lesional cells. The patterns of CD117 reactions (membrane, cytoplasmic or paranuclear, so-called Golgi-type) were also noted. Tumors were stratified based on CD117 reactivity into three groups: 1) less than 15% of the tumor cells are positive; 2) the ratio of CD117 reactive tumor cells is more than 15 but less than 30%; and 3) more than 30% of the cells are positive.

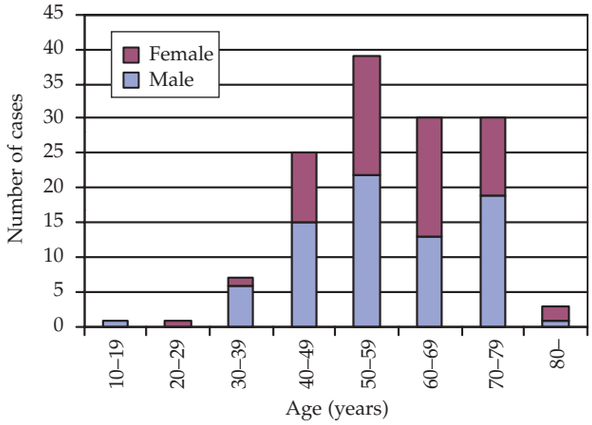

Figure 1. *Age and sex distribution of 136 patients with GIST*

Results

A total of 150 samples of 136 patients were studied. Of these cases, 120 were primary tumors, 12 metastatic and 4 locally recurrent lesions. In fourteen cases two samples per patient were evaluated; for example, hepatic metastases or surgical specimen following biopsy.

The referral diagnoses included GIST or suspicion of GIST (n=93), malignant schwannoma/MPNST (n=6), benign schwannoma (n=6), leiomyosarcoma (n=8), leiomyoma (3), mesenchymal tumor (n=1), pleomorphic rhabdomyosarcoma (n=1), malignant neuroendocrine tumor (n=1), carcinosarcoma (1). Thirteen cases arrived without diagnosis, and the authors primarily diagnosed the remainders. In some cases more than one diagnostic possibilities were raised by the referring pathologists.

It has to be mentioned that a relatively large series of cases was sent to the center with the diagnosis or with the suspicion of GIST, however, after revision other diagnoses such as dedifferentiated (spindle-cell) liposarcoma (1), malignant carcinoid (1), leiomyoma (9), leiomyosarcoma (9), schwannoma (1), mesenteric fibromatosis (3), inflammatory fibroid polyp (3), dedifferentiated carcinoma (5), malignant melanoma (1), mesothelioma (1), dedifferentiated pleomorphic sarcoma (5) or solitary fibrous tumor (3) were confirmed. These cases were not included systematically in this study, but they serve as illustrations for differential diagnoses.

Clinical features

The age and sex distribution of the 136 patients is shown in *Figure 1*. The age was corrected in recurrent and metastatic cases to the time of detection of primary lesions, if the data were reliable. There were 76 males (55.8%) and 60 females (44.1%). The patients' age ranged from 19 to 88 years (median 59 years, mean 59.2 years). Ten patients (7.2%) were 40 years old or younger, the youngest of them a 19-year-old man.

Information regarding presenting symptoms and patient's history were available in 35 cases. The tumors most commonly presented with GI bleeding (14 cases), often with acute bleeding, such as gastric hemorrhage/hematemesis (7 cases) or melena (8 cases), and occasionally with chronic anemia (3 cases). Eleven cases caused diffuse abdominal symptoms, sometimes with externally palpable tumors (in some cases the patients palpated their own tumors). In six cases the leading symptom was weight loss, up to 21 kg. Three cases were operated on an emergency basis due to intestinal obstruction. Seven cases were discovered during routine medical examination for other reason (gynecological examination, ultrasonography, gastroscopy etc.). One case was discerned during acute laparotomy that was preceded by suicidal abdominal knife puncture.

In twelve cases metastatic samples were analyzed, and the sites of primary tumors in these cases were stomach (5 cases) and small bowel (4 cases), while the exact localization of the primary lesion was not known in 3 cases. Two patients had multiple GISTs (one in the small intestine, one in the stomach). Two GISTs in the small intestine caused multiple peritoneal metastatic nodules, and one in the jejunum formed satellites adjacent to the primary lesion

Table 2. **Localization of primary and metastatic GISTs**

Localization of examined primary tumors	*Localization of known metastases*	*No. of metastatic cases*
Stomach (61)	liver	11
	abdominal cavity (peritoneum, mesenterium, spleen)	12
	bone	1
	subcutaneous adipose tissue	1
Small bowel (38)	liver	13
	abdominal cavity (peritoneum, mesenterium)	12
	bone	1
	lung	1
	pancreas	1
Large bowel/rectum(11)	liver abdominal cavity (minor pelvis)	1 6
	lung	1

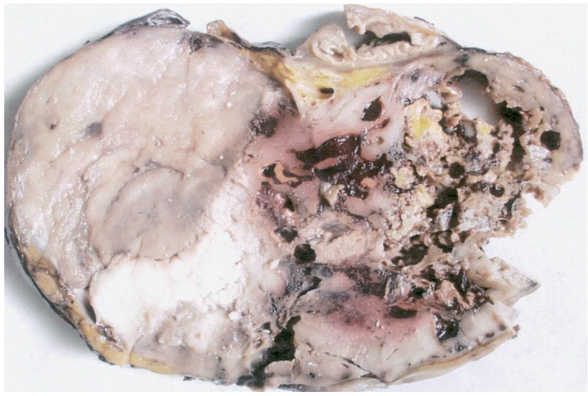

Figure 2. *Small intestinal GIST. The tumor involved the entire mesenteric region. Note the large necrotic and hemorrhagic areas.*

clinically mimicking multiple GISTs. In four cases the primary tumor and hepatic metastases were simultaneously resected. Four patients had locally recurrent GISTs. The mean time to recurrence were 5, 9, 12 and 17 years, respectively. The localization of known local and distant metastases from different primary GISTs are summarized in *Table 2*.

Gross evaluation

GISTs involved the stomach in 50.4% (61 of 121 primary tumors) and the small intestine in 31.4% of cases (38 of 121). The small intestinal GISTs were found in the duodenum in 7, in the jejunum in 11, and in the ileum in 4 cases. The site was small intestine but unspecified in 16 cases. The colon or the rectum was the site of origin in the case of 11 of 121 primary tumors (9.4%), 3 and 8 cases, respectively. Abdominal cavity was indicated as tumor site in 10 cases, without further specification in 8 cases. In 2 cases the large size or the multiple organ involvement made the assessment of the origin impossible. On 3 occasions the possibility of extragastrointestinal origin was raised, but the lack of exact clinical data impugn this.

The localization of metastatic GISTs sent to second opinion were liver (8), abdominal wall (1), omentum (1) and subcutis (1). Locally recurrent cases were localized to the stomach (1) and small bowel (3).

The primary and recurrent tumors ranged in size from 0.5 to 30 cm (mean 8.3 cm). In some cases the size was not available, either because the original gross description was not sent, or the size of the tumor was vaguely noted (i.e. “huge”). These cases were interpreted as more than 10 cm, high-risk lesions.

At the time of the operation eight tumors of the stomach invaded the retroperitoneum, mesocolic adipose tissue or the greater omentum, or extended to the hilar region of the spleen. Similar retroperitoneal or mesenteric extension were seen in seven small bowel (*Figure 2*) and two large bowel GISTs, while two rectal GISTs extensively infiltrated tissues of the minor pelvis. One duodenal GIST penetrated the pancreas.

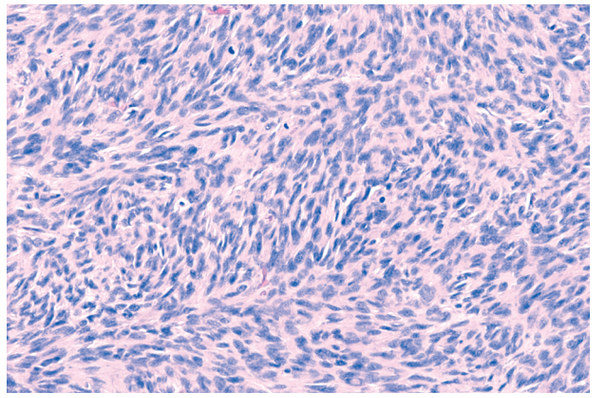

Figure 3. *Highly cellular, mitotically active spindle cell GIST. The microscopic appearance resembles leiomyosarcoma. x100*

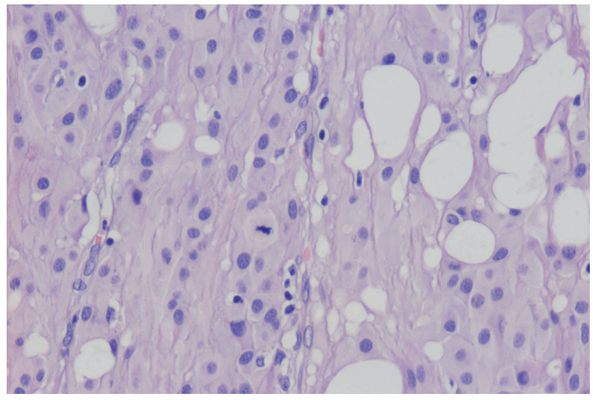

Figure 4. *Epithelioid GIST composed of polygonal cells with pale eosinophilic cytoplasm. x100*

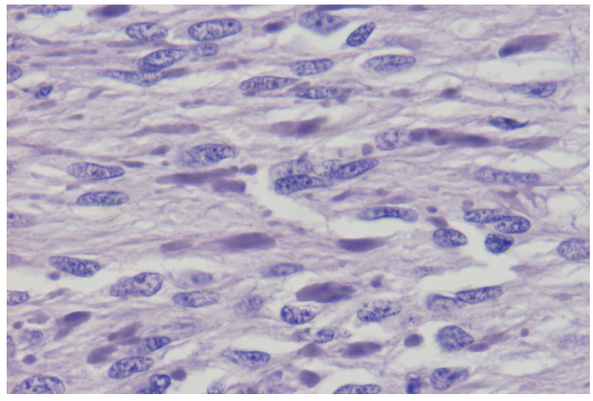

Figure 5. *Presence of skeinoid fibers in a small intestinal GIST. x200*

Table 3. **Occurrence of defined histologic features of GISTs by localization**

Localization	*Cell type spindle/ epithelioid/mixed*	*Specific histological pattern*			*Myxoid change*	*Coagulation necrosis*	*Skeinoid fibers*	*Vascular pattern sinusoidal*	*Hyalinization (perivascular or stromal)*
		Nuclear palisading	*Storiform pattern*	*Paraganglioma-like appearance*					
Stomach (n=61+1 rec.)	47/5/11	16	2	3	28	17	1	19	16
Small intestine (n=38+3 rec.)	27/2/12	6	6	2	17	11	14	24	9
Colon/rectum (n=11)	7/0/4	3	2	1	1	6	0	2	2
Abdominal cavity (n=10)	4/3/3	2	0	1	6	6	1	5	1
Metastatic (n=11)	7/1/3	0	1	0	6	0	0	9	1

The locally recurrent cases (1 gastric and 3 small intestinal) were added to the appropriate primary.

Endophytic, predominantly luminal growth was present in 8 gastric GISTs. In several cases the tumors were attached to the outer surface of gastrointestinal organs, presenting as an exophytic mass in the abdominal cavity. This phenomenon was present in two ventricular and three small intestinal cases. This series included one triple gastric and two multiple small intestinal cases.

Microscopic evaluation

The occurrence of selected histologic features in tumors stratified by localization is shown in *Table 3*. Ninety-two cases were classified as having a spindle cell or predominantly spindle cell pattern (*Figure 3*), with only minute foci of epithelioid areas. Epithelioid cytology was dominant in 11 cases among which 6 had purely epithelioid cytology (*Figure 4*). Mixed spindle and epithelioid pattern, where the two cell types were equally present, was seen in 33 cases. Skeinoid fibers were present in 14 GISTs localized to the small bowel (*Figure 5*), one localized to the stomach, and one abdominal case, where the exact origin of the tumor was indiscernible because of large tumor size and multiple organ involvement. Coagulation necrosis was seen in 40 primary GISTs, and calcification, sometimes adjacent to or within the necrotic areas, were present in 4 cases (*Figure 6*). Ulceration observed by microscopic examination was common in GISTs involving the stomach, small intestine or colon-rectum (36 of 110 cases, 32.7%), even though in several cases the mucosa was not present on the slides. GISTs characteristically have well-circumscribed, pushing borders, however, partially infiltrative borders in less differentiated cases and, interestingly, in smaller, intramural cases were also observed.

Due to the variable histological appearance of GISTs it is hard to say what features can be designated as unusual or striking. In this study we recorded some degree of myxoid change in 58 cases (42.6%), occasionally with cystic transformation, especially in the abdominal cases. More than minute foci of stromal hyalinization were present in 29 cases (21.3%). Nuclear palisading (*Figure 7a*). suggestive of neurogenic tumors appeared in 27 GISTs, most often in small intestinal localization (44.7%). Nuclear palisading was recorded only if it gave a neurogenic phenotype to the tumor. More unusual features, such as storiform pattern (*Figure 7b*) or paraganglioma-like appearance with "Zellballen" or small nodular arrangement of the cells (*Figure 7c*), were present in 11 and 7 cases, respectively. Small cell areas resembling carcinoid or poorly differentiated neuroendocrine tumor were present in 5 cases. Mild diffuse lymphoid infiltrate was often present, but large lymphoid aggregates within the tumor were observed only in 5 cases.

Nuclear pleomorphism was usually moderate, but scattered bizarre nuclei or 'monster' cells were often seen (*Figure 8*). Vesicular nuclei, prominent eosinophilic nucleoli or intranuclear pseudoinclusions, multinucleated or ganglion-like cells were not characteristic features, but all have been observed in isolated cases. Occasionally, the cells acquired a prominent cytoplasmic vacuole resulting large clear cell areas.

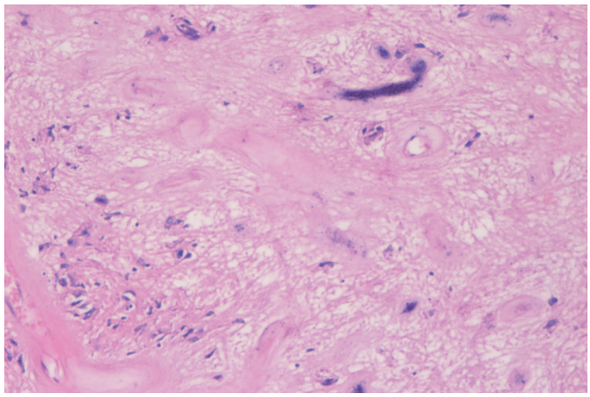

Figure 6. *Extensively necrotic GIST with foci of calcification. x100*

The mitotic count could not be reliably established in four cases that were small and fragmented. Two small intestinal cases were sent without description of tumor size, but based on mitotic activity, they were assessed as intermediate or high risk GISTs. In two fragmented samples the mitotic count was not countable, but these tumors were clinically malignant. In two small specimens the mitotic activity was extrapolated to 50 HPFs from 5-10 HPFs. In primary and recurrent GISTs the mitotic activity was variable, ranging from less than 1 to 400 mitotic figures/50 HPFs (mean 29.1, median 10). The only case with 8/1 HPF mitotic activity was a recurrent small intestinal case. The mitotic rate was <5/50 HPFs in 39 cases (32.7%); and 26 tumors (21% of all primary and recurrent cases) had more than 50 mitoses/50 HPFs. The prognostic grouping of primary tumors, based on tumor size and mitotic activity, is seen in *Table 4*.

Among histological features vascular patterns of GISTs were also noted. A peculiar feature of GISTs was the presence of dilated, thin-walled sinusoidal channels. These prevailed irrespectively of site of the tumor in 59 cases. The presence of hyalinized blood vessels was also typical (*Figure 9a*), often in association with extensive stromal hyalinization. Seldom hemangioma-like proliferations were also observed (*Figure 9b*). Distinctive vascular pattern manifested in some cases as minute foci of Masson-like papillary endothelial hyperplasia or partial hyperplasia of vessel walls (*Figure 9c*).

There were 7 endoscopic samples in this series. Five small GISTs were resected with endoscopic loop, and two specimens contained small tumor fragments. The number of excisional biopsies from inoperable abdominal or retroperitoneal tumor was four.

The number of core needle biopsies were 10, 3 from large abdominal primary tumors, 3 from hepatic metastases of known GISTs, and 4 from hepatic metastases of formerly not known GISTs.

Immunohistochemical findings

The immunohistochemical findings are summarized in *Table 5*. CD117 (c-kit) positivity was documented in 133 cases. The reactions were interpreted as positive if the membrane, the cytoplasm or the paranuclear region was reactive. The predominant pattern was diffuse cytoplasmic positivity in 85%, and strong membrane reaction predom-

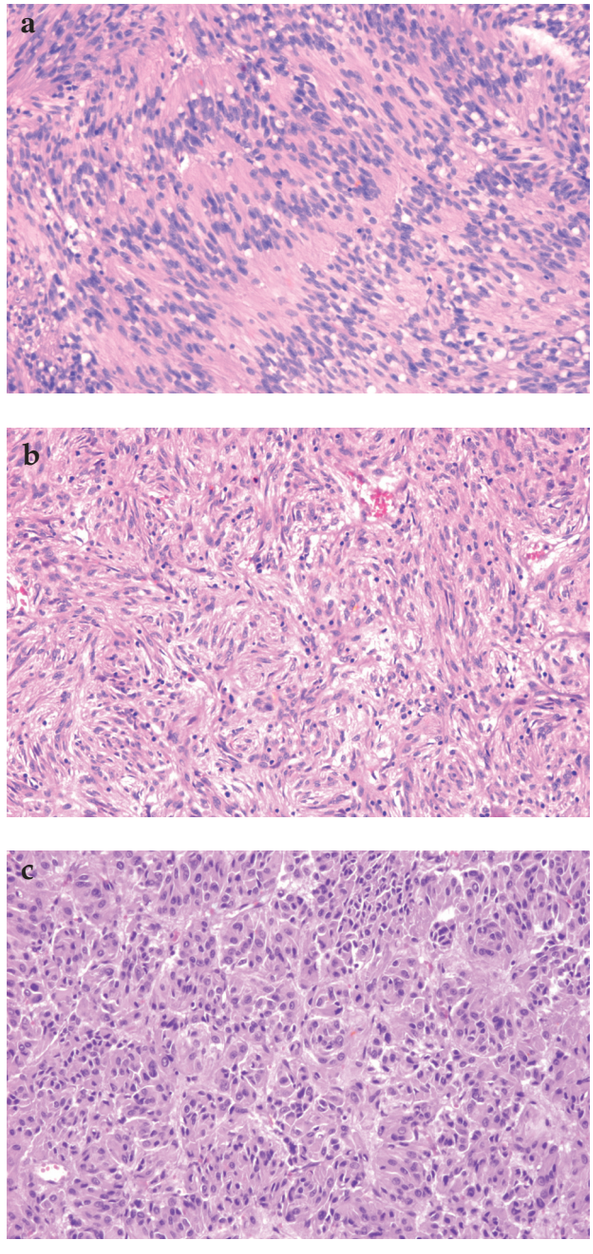

Figure 7. *Variable histological features of GIST: prominent nuclear palisading simulating schwannoma* ***(a);*** *storiform pattern mimicking solitary fibrous tumor* ***(b);*** *so-called 'Zellballen' arrangement reminiscent of paraganglioma* ***(c).***

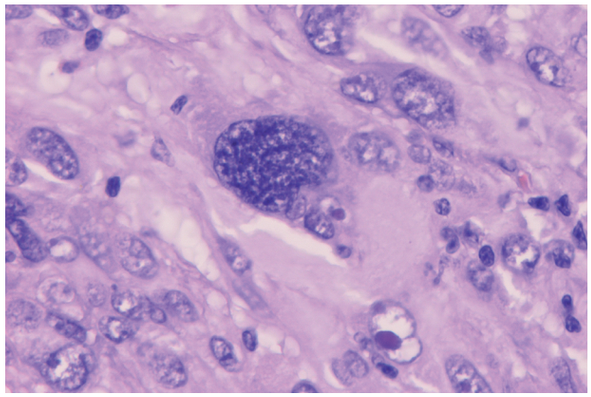

Figure 8. *Pleomorphism is not a characteristic feature of GIST, but bizarre 'monster' cells are often present. x400*

inated 15% of the cases. More or less dot-like positivity was observed in 30% of the cases (*Figure 10*). No pure Golgi-like reaction was present without membrane or cytoplasmic reactivity. Only five cases showed c-kit positivity in less than 30% of the tumor cells. One of the three c-kit negative cases was CD34 positive. In these cases other reactions but vimentin were also negative.

CD34 positivity was seen in 91 of 130 cases (70%), including the above mentioned c-kit negative case. CD34 positivity was expressed in more than 30% of tumor cells in most cases. Alpha-smooth muscle actin reactions were performed on 126 cases, and 50 (39.6%) were positive.

Table 4. **Prognostic assessment of 112 primary tumors*[$]**

	Size	*Mitotic count*	*No. of cases*			
			S	*G*	*C*	*A*
Very low risk	<2 cm	<5/50 HPFs[§]		4		
Low risk	2-5 cm	<5/50 HPFs	6	6		
Intermediate risk	<5 cm	6-10/50 HPFs		2	1	
	5-10 cm	<5/50 HPFs	2	5		1
High risk	>5 cm	>5/50 HPFs	2	7	1	
	>10 cm	Any mitotic rate	17	19	6	6
	Any size	>10/50 HPFs	8	14	3	2

* The first line of prognostic assessment was the tumor size. E.g. if a tumor was larger than 10 cm and had mitotic count over 10/50 HPFs, it was stratified to high-risk >10 cm, any mitotic rate' group.

[§] HPF = high power field (x 400 microscopic magnification)

S = small intestinal; G = gastric; C = colon/rectum; A = abdominal

[$] Prognostic assessment of 8 primary tumors was ambiguous therefore they were excluded

Only one case of the examined 112 was positive for desmin. Seven tumors of the examined 121 had S100 positive tumor cells. In 64 cases h-caldesmon was also tested, and 39 cases (60.9%) proved to be positive, most of them with >30% of tumor cells positive (*Figure 11*). Cytokeratin (AE1/AE3) reaction was performed in 7 cases without positive result. Five tumors that were tested for vimentin were positive.

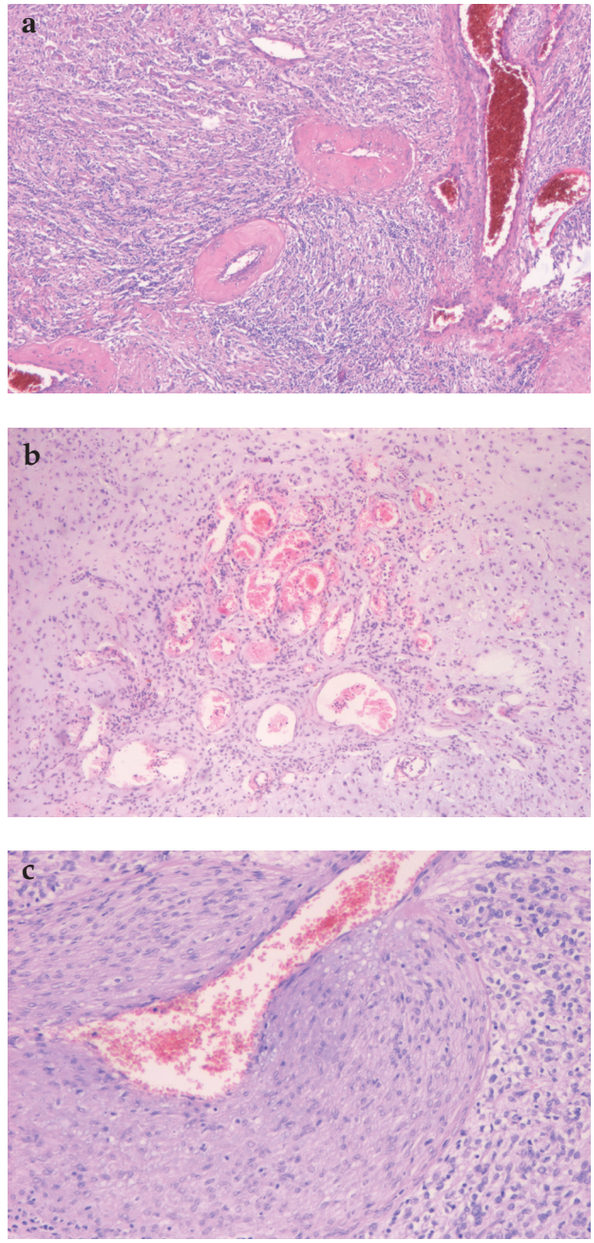

Figure 9. *Different vascular changes in GIST are often present, such as hyalinization of blood vessel wall* ***(a)****; but hemangioma-like changes* ***(b)****; or hypertrophy of vessel wall* ***(c)*** *are unusual features*

Table 5. **Summary of the immunohistochemical findings (the number of cases available for different studies varied)**

Antibody	*>30% +*	*15-30% +*	*5-15% +*	*Negative (<5% +)*	*Positive/ total*	*Percent positive*
CD117 (c-kit)	128	5	0	3	133/136	97.8%
CD34	80	5	6	39	91/130	70%
α-smooth muscle actin	24	15	11	76	50/126	39.6%
Desmin	1	0	0	111	1/112	0.9%
S100 protein	2	2	3	7	7/121	5.7%
h-Caldesmon	31	7	1	25	39/64	60.9%
Vimentin	5	0	0	0	5/5	100%
Cytokeratin (AE1/AE3)	0	0	0	7	0/7	0%

Discussion

Traditionally, most mesenchymal neoplasms of the gastrointestinal tract were thought to be of leiomyogenic origin and, depending on pleomorphism, cell type and mitotic activity, diagnosed as leiomyoma, leiomyosarcoma or, after the classical work of Stout,[31] as leiomyoblastoma. In the cases of tumors showing prominent nuclear palisading, Schwann cells had been implicated as possible precursors. In 1983 Mazur and Clark[19] ushered the term 'gastrointestinal stromal tumor', and they suggested the myenteric plexus as a possible origin. In the nineties pathologists classified further stromal tumors as myogenic, neurogenic, dual or null type, depending on the expression or negativity of smooth-muscle actin, desmin and S100, and in this period several arguments could be read about this topic.[13] The recognition of CD34 positivity of GISTs enhanced the diagnostic appreciation,[26,27] however, only 60-70% of GISTs are CD34 positive, and some tumors of leiomyogenic or Schwannian differentiation can be CD34 reactive. The old argument about the neurogenic or leiomyogenic nature of GISTs was solved (similarly to Gordian knot) with the recognition that GISTs show differentiation toward interstitial cells of Cajal either at ultrastructural or immunohistochemical level.[15] The proposed change of the name from stromal tumors to the formally more logical term gastrointestinal pacemaker cell tumors, or GIPACT, however, could not replace the widely accepted term GIST. Simultaneously, another group of researchers clarified the genetic background of this tumor, identifying activating mutation of c-kit in GISTs.[12] Gastrointestinal autonomic nerve tumors (GANTs), based on their immunohistochemical CD117 positivity and frequent c-kit gene mutation, are now regarded as morphologic variant of GIST.[18] Nevertheless, the c-kit (CD117) is negative or non-reactive in 2-8% of GIST cases. On genetic level these tumors form a heterogeneous group. One subset of this group shows c-kit mutation, while the other contains intact (wild-type) c-kit gene. In the latter subgroup PDGFRA (platelet-derived growth factor receptor A) mutations are responsible for abnormal kinase function. The c-kit mutant tumors will respond to imatinib therapy, while the PDGRFA mutants are believed resistant.[2] The impact of these observations to everyday practice is not entirely clear at this time.[20] A group of researchers developed a new marker, called DOG1, which is expressed in 97.8% of GISTs, irrespectively of c-kit or PDGFRA mutation status.[33]

The prediction of the biological behavior of GISTs is based on two prognostic factors, tumor size and number of mitoses. The proposed consensus risk grouping is applied at GIST categorization instead of definitive benign or malignant classification.[8] The rationale of this approach is the fact that low-grade lesions occasionally metastasize.[32] Some authors attempted to define more objective parameters (e.g. MIB-1)[11] because of inaccurate mitotic count, or complete the risk grouping with other parameters (e.g. localization), but at the moment the consensus risk grouping seems most useful. The high number of metastatic gastric GIST cases in our series queries the conception that GISTs originated from stomach behave more favorably than small intestinal ones.

Differential diagnosis of GIST in endoscopic samples is a relatively neglected field of the literature. This is an important aspect, since the vast majority of GIST patients have abdominal complaints and melena, and can be subjected to endoscopic examinations. GIST can be reached by endoscopy when it is small and polypoid, or when a larger tumor infiltrates the mucosa and/or ulceration occurs. Major differential diagnostic problems in these circumstances are submucosal leiomyoma, inflammatory polyps, inflammatory myofibroblastic tumors and schwannomas.

Submucosal leiomyoma is a relatively infrequent tumor in the GI tract. It is characterized by a bright eosinophilic cytoplasm, elongated bland nuclei and lack of mitotic figures, all uncharacteristic for GIST. This tumor is frequently associated with the muscular mucosa. Perinuclear vacuoles can be present in leiomyoma and GIST as well. The diagnosis of leiomyoma is based on the characteristic immunophenotype: desmin, α-smooth muscle actin and h-caldesmon positivity, and CD117 and CD34 negativity.

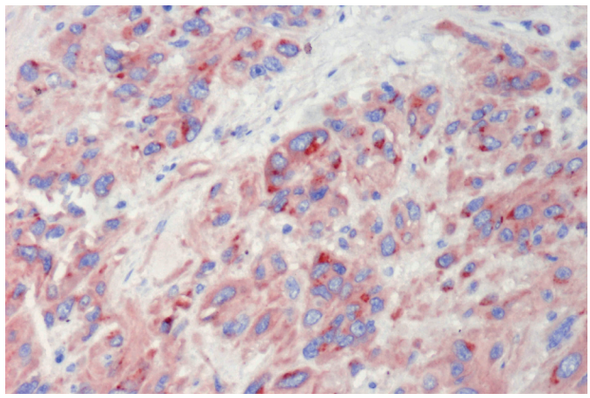

Figure 10. *A jejunal GIST with strong dot-like CD117 positivity and less intense cytoplasmic staining. x200*

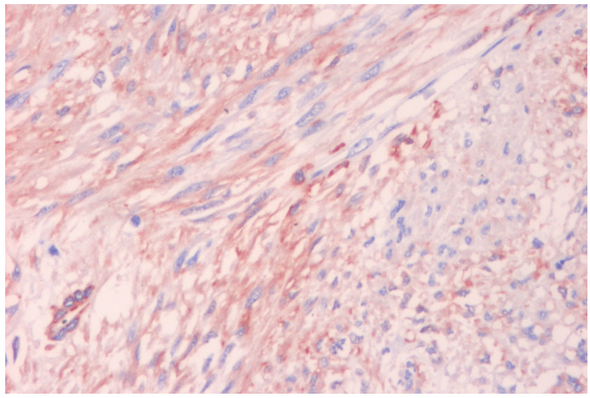

Figure 11. *Ventricular GIST showing strong, intense h-caldesmon positive reaction. Note the positivity of blood vessels on the left side. x200*

Among the cases referred as GIST we have relatively often seen inflammatory fibroid polyps. Inflammatory fibroid polyps are benign lesions, typically consisting of fibroblast-like spindle cells, granulation tissue-like vascular area and inflammatory infiltrate. They are characterized by onion skin-like arrangement of spindle cells around vessels and glands. The majority of cases are CD34 positive but never CD117 reactive.[3]

In fact, gastrointestinal schwannomas are extremely rare and only case reports and a few small series have been published.[16,24] The smaller, polypoid schwannomas can be resected with endoscopic loop. Because features characteristic of schwannomas outside of GI tract, such as nuclear palisading, Verocay bodies and hyalinized vessels, are often absent, suspicion of GIST may be high in these cases. Fortunately, the strong nuclear and cytoplasmic S100 positivity and CD117 negativity help to separate schwannomas from GISTs. Based on the evaluation of NF1 and NF2 tumor suppressor genes, GI tract schwannoma is reckoned as an entity differing from the conventional form.[17]

In contrast to earlier practice, samples from surgically resected gastrointestinal mesenchymal tumors have been mainly referred to the centers as GISTs or possible GISTs. Naturally, in places where it is not possible to perform c-kit immunohistochemistry, or the primary tumor was operated on several years before, other diagnostic possibilities are more often raised. Differential diagnoses of GISTs in surgical and in endoscopic samples are partially overlapping, but this is modified by the fact that in surgical specimens pathologists more often face large, advanced tumors. The differential diagnostic problems greatly depend on the histological appearance of the given GIST, especially on the presence or absence of specific histological patterns or cell types (e.g. epithelioid or spindle).

Similarly to the differential diagnosis of endoscopic biopsy, leiomyogenic tumors turn up again, namely true GI tract leiomyosarcomas. Typical leiomyosarcomas are composed of spindle-shaped tumors cells that have elongated, often cigar-shaped nuclei and bright eosininophilic cytoplasm. GISTs on H&E sections often have closely similar, sometimes identical leiomyogenic appearance. With the use of c-kit immunohistochemistry and based on the fact that GISTs are exceptionally positive for desmin, the question is generally easily answerable. However, it has to be mentioned that h-caldesmon, a useful marker for the identification of leiomyogenic lesions in other localization,[1] is useless in this context, because GISTs in our series were positive in 60.9%, reflecting leiomyogenic part of differentiation toward Cajal cells.

Interestingly, large sized, spindle cell-type GISTs more often show neurogenic pattern (the above mentioned nuclear palisading, Verocay bodies, hyalinized vessels) than true GI schwannomas. S100 positivity in our GIST series occurred only in 5.7%.

Intraabdominal fibromatosis, especially the mesenteric form involving bowel wall can cause severe differential diagnostic problems. Fibromatoses are composed of monotonous spindle cell proliferation. The cells are arranged to long sweeping fascicles within collagenous, often keloidal stroma. Cytological variability and mitotic activity are generally minimal. Inoperable cases, especially if the biopsy sample is small, have to be evaluated carefully, because certain anti-CD117 antibodies may result in positive cytoplasmic staining leading to false GIST diagnosis.[36]

From a series of CD117 positive tumors (*Table 6*) one has to reckon with the possibility of extension of poorly differentiated ovarian cancer to the bowel wall or with melanoma metastasizing to bowel wall or primary GI tract melanoma. In cases of ovarian cancer the knowledge of relevant clinical data and searching for better differentiated tumor area and cytokeratin positivity can help. Poorly pigmented GI tract melanoma, spindle or epithelioid cell type might be a mimicker of GIST. Completing the S100

Table 6. **C-kit/CD117 positive tumors***

Gastrointestinal stromal tumor (GIST)
Mast cell neoplasias
Malignant melanoma (reactivity decreases with progression)
Seminoma/dysgerminoma and intratubular germ cell neoplasia (IGCN)
Endometrial cancer
Follicular and papillary thyroid cancer
Merkel cell carcinoma
Adenoid cystic carcinoma of salivary gland
Malignant glioma
Angiomyolipoma
Acute myeloid leukemia
Small cell lung cancer

*The list is not complete and contains only the mostly positive tumors.

immunohistochemistry with Melan-A and/or HMB45 support the diagnosis of melanoma.

Solitary fibrous tumors occasionally occur in the peritoneal cavity. This spindle cell neoplasm is described as having a so-called patternless pattern, but storiform arrangement of featureless spindle cells can occur. Similar storiform arrangement in GIST can also be seen, and a further common feature of both lesions is CD34 positivity. However, solitary fibrous tumors do not stain with CD117.

Neoplastic cells of GISTs sometimes form smaller structures similar to 'Zellballen' of paragangliomas. In these cases the use of neuroendocrine marker and S100 positivity of sustentacular cells, in addition of CD34 and CD117 negativity, help us to differentiate paraganglioma from GIST.

GISTs show a picture of a dedifferentiated tumor only exceptionally. Notwithstanding, in recurrent GISTs the rising of anaplasia and mitotic activity can result in the appearance of a pleomorphic, dedifferentiated sarcoma. In these cases the evaluation of CD117 reactivity is essential, because these dedifferentiated GISTs can also respond to adequate imatinib therapy.

During the evaluation of histological features we were not able to observe such high occurrence of hemangioma-like proliferation as described by Miettinen and colleagues.[22] However, the frequent sinus-like or hyalinized vasculature of GIST was often accompanied by intraluminal thrombotic processes, and in a few cases with Masson-like proliferations. The focal or circumferential vessel wall hyperplasia represents a variant of vasculature of GIST too.

In several cases it was problematic to determine the exact origin or to prove the true extragastrointestinal origin of the tumor. This is due partly to deficient clinical information, but not negligibly to the number of cases with advanced disease involving multiple organs. The abdominal extragastrointestinal GISTs have to be carefully evaluated, because a minority of cases grow dominantly to serosal cavity easily separable from the serosal surface. These cases can be erroneously interpreted as extragastrointestinal, but in fact represent subserosal mural lesion. Extragastrointestinal GIST can be diagnosed only when no attachment to the serosa of GI tract is present, and the intraoperative and macroscopic description is unequivocally supportive.[28]

Problems with predicting the biologic behavior of GISTs have been mentioned above. From oncological point of view, follow-up of patients operated without metastasis and residual disease needs to be resolved. Proven recurrent GISTs several years (e.g. 17 years) after the removal of the primary tumor emphasize the necessity of oncological care and long-term follow-up.

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