REVIEW

Gastrointestinal stromal tumors: review on morphology, diagnosis and management

EMŐKE FÜLÖP[1)], SIMONA MARCU[1)], DOINA MILUTIN[2)], ANGELA BORDA[1)]

[1)]*Department of Histology, University of Medicine and Pharmacy of Targu Mures*

[2)]*Department of Pathology, Emergency County Hospital, Targu Mures*

Abstract

Gastrointestinal stromal tumors (GISTs) are the most frequent mesenchymal tumors of the gastrointestinal tract. Major advances in their definition and classification and the understanding of their molecular mechanisms have recently been made. These advances have become a model of targeted therapy in oncology. The diagnosis of GISTs relies on histological arguments – proliferation of spindle-shaped cells in 70% of cases, of epithelioid cells in 20%, histological variants are rare –, and on immunohistochemical arguments – expression of CD117 in 95%, usually associated with CD34 expression in 70% of cases. Most GISTs are associated with molecular abnormalities in low target genes: KIT and PDGFRA. The differential diagnosis of GISTs includes the other mesenchymal tumors of the gastrointestinal tract, such as leiomyomas, leiomyosarcomas, schwannomas and intra-abdominal fibromatosis. The evaluation of the prognosis is essential and is based on a simple algorithm using two histoprognostic parameters, tumor size and mitotic index. The treatment of localized GISTs is surgical resection and that of advanced or unresecable GISTs is based on the use of targeted therapy, imatinib, which is a pharmacological antagonist of the c-kit protein. Proper understanding and utilization of the diagnostic criteria and classification of GISTs by pathologists are essential for good patient management.

***Keywords*:** gastrointestinal stromal tumors, mesenchymal tumors, molecular genetics, immunohistochemistry, c-kit protein (CD117), imatinib.

Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal tumors of the gastrointestinal tract. This category includes some tumors previously diagnosed as leiomyomas, leiomyosarcomas or neurogenic tumors such as neurofibromas and schwannomas [1].

Epidemiology

The incidence of GISTs before 2000 is not known, but at present, it is of 15 cases to one million in the USA and of approximately 11 cases to one million in Northern European states (Sweden, Iceland), with a prevalence of 10–20 cases to 1 million [2, 3]. Although they are the most frequent mesenchymal tumors occurring in the digestive system (80%), they represent approximately 3–5% of all soft tissue sarcomas, respectively 3% of gastrointestinal tumors.

They can develop in any part of the digestive system, from the esophagus to the rectum. The most frequent localizations are the stomach (60%) and the small intestine (20–30%), especially the jejunum and the ileum. Localizations like the large intestine (5%) and the esophagus occur only in 2–5% of cases. Stromal tumors localized outside the gastro-intestinal tract, such as gallbladder or the pancreas, are exceptional. The mesenteric, omental or retroperitoneal localizations represent in most of the cases metastases or the extent of a primary GISTs localized in the gastro-intestinal tract [4, 5]. The majorities of GISTs develops until the fifth or sixth decade, and are rarely diagnosed in patients younger than 40 years. GISTs can also occur in children but only exceptionally, the occurrence rate being under 1% it usually develops in the second decade, with predilection for females, gastric localization and epithelioid variant as morphological aspect [6, 7]. No sex related predilection has been demonstrated (although some data indicate a predominance of GISTs in males), which is also valid concerning race, ethnicity, occupation or specific geographical distribution.

Histogenesis and molecular genetics

GISTs represent a special group of mesenchymal gastro-intestinal tumors with a supposed origin in the interstitial Cajal cells (ICC). This hypothesis is sustained by the fact that, from an immunhistochemical point of view, ICC and GISTs present common cell markers. ICC normally expresses CD117 – c-kit while the marker with the highest sensitivity and specificity for GISTs is also represented by the protein c-kit – CD117 [8]. Interstitial Cajal cells are localized in the muscular layer of the digestive tract, including sphincters, around the submucosal and myenteric nerve plexus, especially in the distal part of the stomach and the proximal small intestine. These cells have a

pacemaker role in the regulation mechanism of peristalsis, as they are interposed between the autonomic nervous system and the smooth muscle cells.

It is a well-known fact that most of GISTs are associated with molecular anomalies of two target genes: c-kit (which codifies the kit protein) and PDGFR (which encodes the A chain of the PDGF receptor) [9]. The c-kit protein is a transmembranary receptor with tyrosine kinase activity. Its specific ligand is the stem cells growth factor (SCF). The interaction between c-kit protein and its ligand determines the protein dimerisation, which, in turn, will trigger the phosphorilation and activation of the intracytoplasmic domain of the tyrosine kinase. The activation of this function will allow the kit protein to phosphorilate all intracellular proteins that ensure signal transmission. The main consequence of c-kit protein activation is the induction of cell proliferation and cease of apoptosis. Genetic mutations will allow the intracellular autophosphorilation in the absence of the ligand.

Most kit mutations in GISTs involve exon 11 (60–70%), which is a juxtamembranar domain with regulatory function. Other mutations in decreasing order of frequency are the mutations of exon 9 (9%), 13 (1%), and 17 (1%). Recent studies have demonstrated that GISTs with mutations on exon 11 are the most sensitive to the specific treatment with imatinib, while GISTs with mutations on exon 9 or 13 have a much lower sensitivity. GISTs with mutation on exon 17 represent the specific category of tumors that present primary resistance to imatinib [10, 11].

The mutations regarding PDGFRA gene in GISTs are localized at the level of the exons 18, 12 and 14. Most GISTs with mutations on this gene have a gastric localization with an epithelioid histological aspect, and only a few are localized in the duodenum. Over 80% of mutations in PDGFRA are localized at the level of exon 18 and represent the category of GISTs with primary resistance to imatinib. Mutations at the level of exon 14 are much less frequent (6%) and are usually associated with a less favorable prognosis, while the mutations at the level of exon 12 are the rarest (1%), but they are the most sensitive to specific treatment [12, 13].

Determining these mutations in everyday practice in order to establish the diagnosis is not considered necessary, with the exception of those GISTs that are CD117 negative. Instead, genetic determinations showed their usefulness in establishing GISTs response to the treatment and also in establishing the evolution and prognosis of these tumors.

Clinical manifestations

The clinical signs of GISTs are very variable and depend on the localization and the size of the tumors. Those with intestinal localization are smaller than those of the stomach. Small size GISTs are discovered incidentally, by means of imagistic examination, endoscopy or during a surgical intervention for other causes (gallbladder, gynecological operations, surgical interventions for gastric or intestinal lesions).

Symptoms are related to the tumor mass (abdominal pain, discomfort, distension of the abdomen, palpable abdominal mass, occlusive syndrome) or to anemia (because of occult or manifest gastro-intestinal hemorrhage through mucosal ulcerations). In over 25% of the patients, the tumor rupture can cause acute hemorrhage of the intestinal tract or in the peritoneal cavity.

Less than 5% of GISTs are found as components of syndromes like: neurofibromatosis type I (NF I), Carney triad or familial GISTs syndrome. Usually in the case of the syndrome in which patients with NF I also develop a stromal tumor, this is localized with predilection in the small intestine; they are numerous, small tumors with a decreased mitotic activity, with no clinical signs [14, 15]. The Carney triad, described by Carney, consists of GISTs together with paraganglion and pulmonary chondroma. The stromal tumors in this triad tend to develop exclusively in the stomach, have an epithelioid histological aspect, and occur in young persons, including children and in 85% of cases in women [16].

Until now, only 12 families have been reported with familial GISTs syndrome worldwide. In all of them transmission of the disease is autosomal dominant and it associates clinically with skin hyperpigmentation, dysphagia and mastocytosis [17].

GISTs evaluation can be done with many imaging methods like: ultrasonography, computed tomography (CT), magnetic resonance imaging (MRI), positron emission transverse tomography (PETT). CT-scan can detect small intestinal tumors and guide the biopsy, is an accessible and sensitive method especially in case of liver metastasis evaluation and also provides useful information about the response to the treatment and of the recurrence [18].

Pathology

Initially, the term GISTs was only a descriptive one, introduced in 1983 by Mazur and Clark to define abdominal tumors that were not carcinomas and that also did not present specific characteristics of smooth muscle or nervous cells tumors [19].

Most of the GISTs occur sporadically, and many cases present themselves as solitary lesions. They have a predominant exophytic growth, along the gastro-intestinal tract, protruding into the abdominal cavity. In small tumors, the above mucous membrane is frequently intact, but in case of large, aggressive tumors, ulceration may occur. In small tumors, the muscle layer of the mucosa seems to be coalescent with the muscular layer, and other times it compresses the muscular layer, from which it is delimited by a thicker collagen band [20]. Sometimes the tumor is centered on its own muscular layer, which will determine the tumor to protrude towards the outer surface of the intestinal wall or to invade the mesentery. Invasion of the organs in vicinity can be pointed out in 1/3 cases. Metastases are frequent in GISTs and have been reported in 50% of the patients. The liver is the organ with the most frequent metastases (65%), followed by the peritoneum (21%). Metastases in lymph nodes, lungs and bones are considered rare.

The tumors are well-delimited, not encapsulated, firm in consistency, whitish. Small lesions have a homogeneous aspect overall section surface, while the large lesions may present zones with necrosis, with hemorrhage and with cystic degeneration. GISTs can have a moderate or high cellularity, and they can be divided into spindle cell, epithelioid, signet ring cell, pleomorphic, oncocytic variants, and with myxoid stroma.

GISTs with spindle cells

Seventy percent of tumors are predominantly of the spindle cell type. This microscopic aspect is specific for the tumors in which the cells are uniform, elongated and densely packed (Figure 1). The tumor may exhibit a storiform, pallisading, or herringbone pattern. The nuclei are monomorphous, flattened, have blunt ends and are bullet or cigar shaped, but they can also be long and pointed (Figure 2). Nuclear pleomorphism is not characteristic for GISTs. Cytoplasm is sparse, basophilic or rarely eosinophilic, and it sometimes contains PAS positive juxtanuclear vacuoles.

They can simulate smooth muscle tumors or tumors of the neural sheath, especially when a pallisade-like aspect of the nuclei occurs (Figure 3). Rich vascularization, hemorrhage, hyalinization, myxoid degeneration or zones with calcification (especially in large tumors) can be encountered.

Excessive hyalinization determines the appearance of eosinophilic collagen globules – skeinoid fibers, which are obvious in GISTs of the small intestine, in tumors with aspect of neural differentiation, and are absent in fibromatous lesions and inflammatory tumor-like lesions. These aspects occur especially in tumors with a lower malignancy potential and is associated with a better prognosis [21, 22].

GISTs with epithelioid cells

This microscopic form can be found in particular in gastric tumors, showing round or polygonal cells, with round or eccentric nuclei, with a perinuclear vacuolization. The tumors consisting of small cells, organized in nests or having alveolar disposition seem to metastasize more frequently. The cells have abundant cytoplasm that may be eosinophilic, amphophilic or clear. The nuclei are usually round with small nucleoli, but scattered multinucleated giant cells or cells with bizarre nuclei can be present (Figure 4). Mitotic figures are rare. Stromal alterations include hyalinization and calcification. In the stomach, most epithelioid GISTs are benign in contrast with small intestine GISTs, where the conspicuous epithelioid component is virtually always malignant [23].

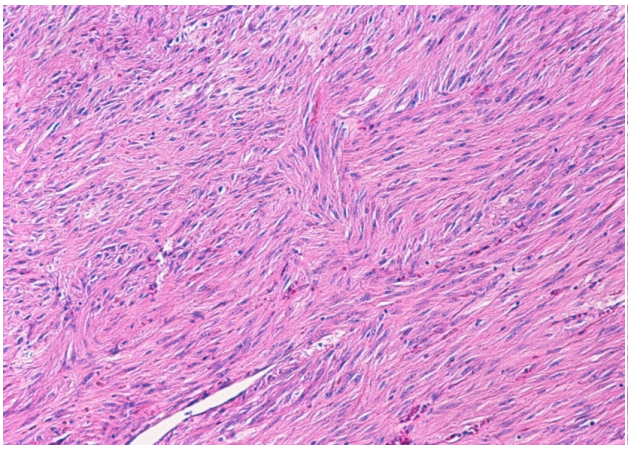

Figure 1 – ***GISTs with spindle cell features and storiform pattern (HE stain, ob. 10×).***

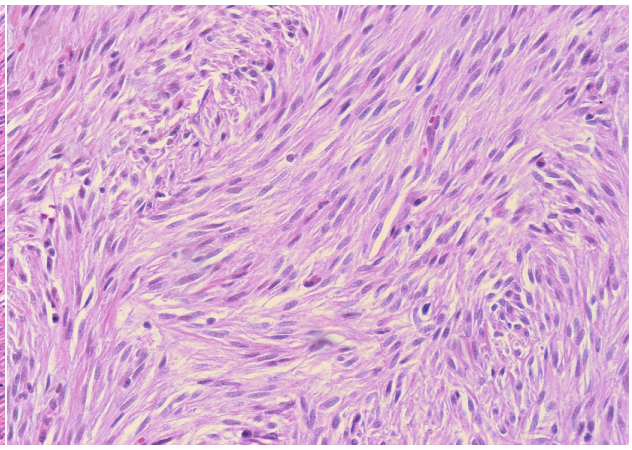

Figure 2 – ***GIST with spindle cell feature, the nuclei have typical blunt ends (HE stain, ob. 20×).***

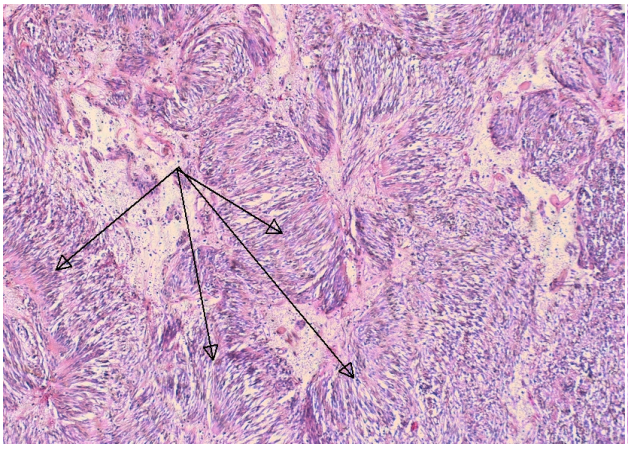

Figure 3 – ***GIST with foci of spindled cell palisades (HE stain, ob. 10×).***

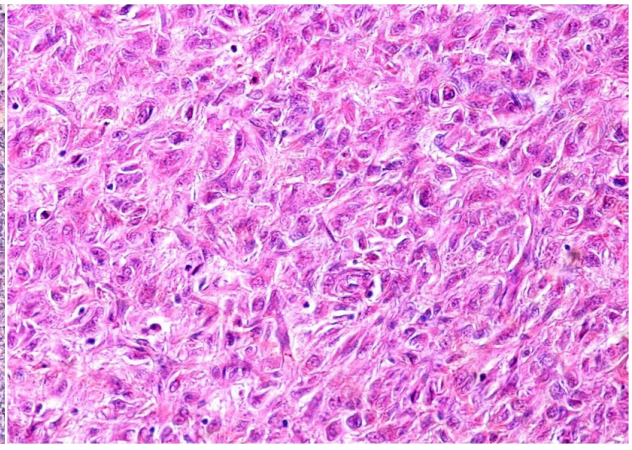

Figure 4 – ***GIST with epithelioid feature, the tumor contain large and round cells arranged in nest or sheets (HE stain, ob. 20×).***

GISTs with signet ring cell feature

These tumors frequently affect women and present as small, well circumscribed gastric, small intestine or rectal serosal nodules. Histologically, the lesions are characterized by a proliferation of large, round to oval cells containing abundant clear cytoplasm with nuclear displacement toward the cellular periphery (Figure 5).

Immunohistochemisty shows strong positivity for vimentin and variable staining for CD34, S100 and actin.

GISTs with myxoid stroma

It occurs more frequently in women. They are well-delimited small sized tumors, with a nodular aspect, localized in the wall of the stomach or intestine. From a histological point of view, they are characterized by a proliferation of large round or oval cells with an abundant, clear cytoplasm and peripheral nucleus. The tumor cells can be found in a myxoid stroma (Figure 6).

Immunohistochemically, they are intensely positive for vimentin and focally positive for CD34, S100 and actin. The metastases of mucinous carcinoma or of other tumors with a similar aspect may be excluded with the help of usual coloration for mucin and IHC methods (CK).

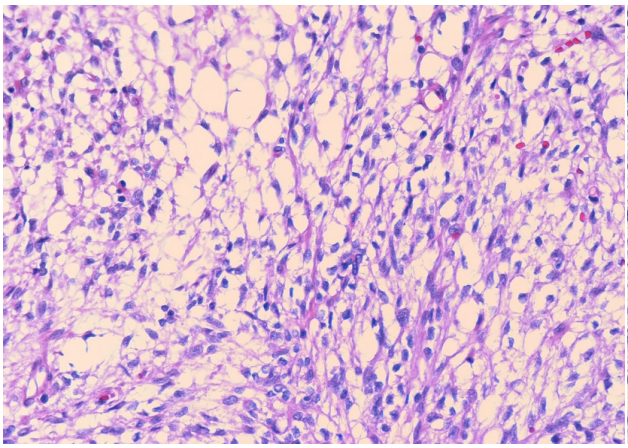

Figure 5 – ***GIST with signet ring features (HE stain, ob. 20×).***

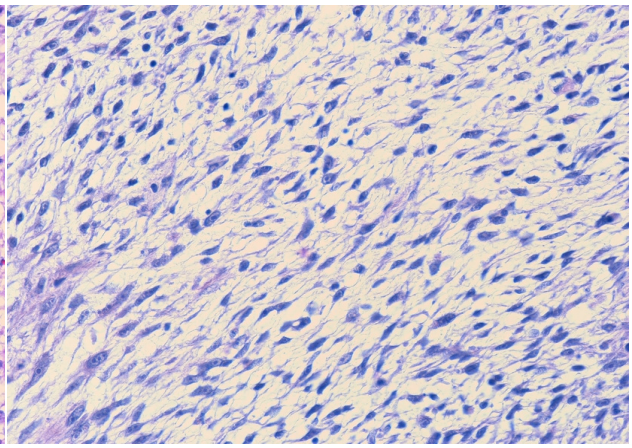

Figure 6 – ***GIST with myxoid stroma (HE stain, ob. 20×).***

GISTs with pleomorph cells

A small part of these tumors shows a marked pleomorphism, high-mitotic activity, with voluminous, irregular nuclei and prominent nucleoli. These tumors can completely or partially lose their immunoreactivity for CD117, making a correct diagnosis difficult to establish.

GISTs oncocytic variant

An abundance of mitochondria has been observed in the cytoplasm of these tumor cells. IHC is typically CD34, CD117 and vimentin-positive.

Gastrointestinal autonomic nerve tumors – GANTs

They are now known to represent a GISTs variant. The main localization is represented by the small intestine, rarely by the stomach, occasionally by the large intestine, esophagus, retroperitoneum and mesentery. It affects mainly the males aged over 60 years. Tumors occurring in young persons and with gastric localization usually accompanies the Carney triad.

The microscopic aspect is similar to the other stromal tumors – epithelial shape, spindle cells with myxoid stroma. The presence of skeinoid fibers is more frequently observed than in other stromal tumors, mitotic activity is variable and frequently lymphoid aggregates can be seen around the tumor cells nests (Figure 7). Their malignant potential is not different from that of GISTs with the same size, histological features and localization.

IHC they are vimentin and CD117-positive, relatively frequently CD34, occasionally S100-positive and SMA-negative [22].

These tumors can be separated from other stromal tumors by studying the ultrastructural aspect of their components. The diagnostic characters include the presence of cells with cytoplasm prolongations that contain microtubules and granules with dense core, with the absence of actin filaments. The cytoplasm prolongations are long and branched. Cytoplasm is rich in SER, intermediary filaments, mitochondria, and RER. The dense core granules are variable in size (100–300 nm) and they have a diffuse disposition.

Immunohistochemistry

C-kit protein

Approximately 95% of GISTs display a positive staining for c-kit (CD117), which is considered a marker with high sensitivity and specificity. The immune staining is variable for other markers too, including: CD34 (70%), smooth muscle actin (50%), neural protein S100 (10%), and desmin (5%).

The intensity of immunomarking for c-kit is variable. In most cases, it is not intense and homogeneous in all tumor cells. There are cases with only a small percentage of positive cells (10–20%). In practice, the minimum percentage of c-kit-positive tumor cells needed to establish the diagnosis of GISTs

has been not yet established. If the percentage is below 10% and the marked cells are isolated or arranged in small groups it is important to differentiate possible tumor cells from mast cells, which are numerous in the chorion of the intestines, respectively from the Cajal cells in the plexus and muscular layer (Figure 8). In these cases, in current practice, it would be very useful to use a scoring system that should include the localization of the tumor, intensity and percentage of positive tumor cells with this immunomarker in order to facilitate the diagnosis [24].

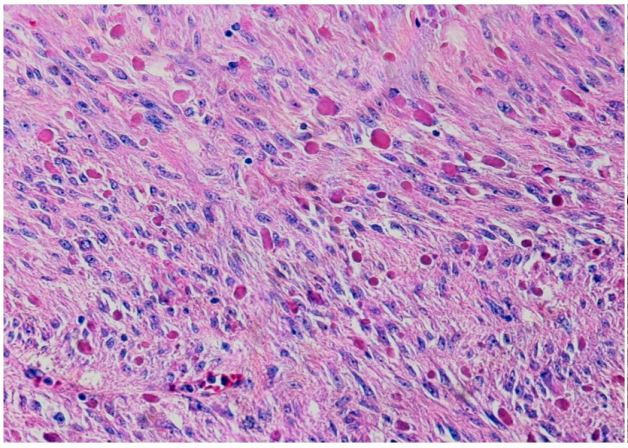

Figure 7 – ***Small intestinal GANTs with characteristic eosinophilic collagen globules (skeinoid fibers) (HE stain, ob. 10×).***

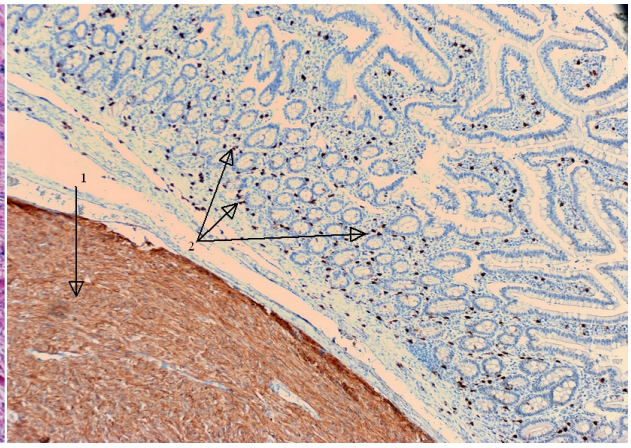

Figure 8 – ***CD117 immunostaining of a GIST arising in intestinal submucosa: 1 – the tumor is strongly positive for the c-kit protein (CD117); 2 – c-kit positive mast cells, which are numerous in the chorion of the normal intestines.***

There are some exceptional cases of c-kit-negative GISTs (5%). Diagnosis of c-kit-negative GISTs will be made with high precaution and only after a thorough analysis and elimination of some causes that might determine the negativity of marking (problems with paraffin-embedding, possible technical errors, cases of GISTs treated with imatinib, metastatic and congenital lesions which are usually c-kit and CD34-negative) [25]. In these cases, a molecular study of the mutations in KIT and PDGFRA will be necessary.

CD117 **is not** specific for GISTs. This marker is also expressed in other tumors like seminoma, malignant melanoma, follicular thyroid carcinoma, lung carcinoma with small cells, oncocytoma and real chromophobic carcinoma, thymic carcinomas and thymomas, angiosarcomas, chronic myeloid leukemia, mast cell tumors, germinal tumors, etc.

Fortunately, the distinction between GISTs and these tumors can be made on histological grounds and with the use of specific markers.

CD34 protein

This protein is another marker used to diagnose GISTs, less sensitive then c-kit, and expressed in 60-70% of these tumors. It is more frequently expressed in stromal tumors localized in the esophagus and rectum (90%) and more rarely in those localized in the small intestine. For a complete immunophenotypical evaluation of GISTs and for establishing the diagnosis some other immunomarkers may be used: smooth muscle actin, desmin, h-caldesmon, S100-protein, vimentin, specific neuronal enolase, glial fibrillary acid protein.

Smooth muscle actin

It is a marker of normal and tumor smooth muscle cells and of myofibroblasts. Approximately 30–40% of GISTs are positive for the protein that is more frequently expressed in tumors with localization in the small intestine than in those with other localizations, and associates with a favorable prognostic.

H-caldesmon

It has been recently introduced among the diagnostic tools in GISTs. It is a protein associated with actin, expressed in normal and tumoral smooth muscle cells (leiomyomas, leiomyosarcomas). The association of a high positivity for h-caldesmon, SMA and desmin will guide the diagnosis towards a smooth muscle tumor, rather than towards a GIST.

S100 protein

Only 5% of GISTs, the GANT variant, are positive for anti-S100 antibodies, especially those localized in the small intestine. A high-positive value will guide the diagnosis towards a schwannoma, which is c-kit negative, or towards a metastasis of a melanoma [26].

Prognostic markers

The mitotic index is an indicator of prognosis in GISTs, therefore, Ki67 is usually proposed as a potential prognostic marker.

Assessment of GISTs biological potential

Before 1999, the diagnosis criteria for GISTs were much debated and sometimes unclear. Tests performed on a large series of GISTs pointed out the following aspects as clinical and pathological factors with severe prognosis: aneuploidy demonstrated with the help of flow cytometry, size of the tumor, presence of coagulation necrosis, a high score for the Ki67 marker and the presence of peritoneal dissemination after first surgical intervention.

A combination of prognostic factors (patient age, tumor size, histological type, degree of necrosis, cellularity, nuclear pleomorphism, mitotic activity, and DNA-analysis) have been used to predict their behavior. An international consensus in 2002 established the fact that in practice, in order to define the risk of aggressivity of GISTs from a pathological point of view, the size of the tumor and the mitotic index should be taken into account [27]. Thus, GISTs of very low risk, low-risk, intermediary risk and high-risk of aggressivity can be distinguished (Table 1).

Table 1 – ***Suggested guidelines for assessing the malignant potential of GISTs of different size and mitotic activity***

Aggressivity risk	Tumor size	Mitotic index
Very low risk	<2 cm	<5/50 hpf
Low risk	2–5 cm	<5/50 hpf
Intermediary risk	<5 cm 5–10 cm	6–10/50 hpf <5/50 hpf
High risk	>5 cm >10 cm any size	>5/50 hpf any mitotic rate >10/50 hpf

hpf – high-powered field

The mitotic index will be interpreted according to the cell type, nuclear atypia and cellularity. GISTs with small intestine localization and with epithelioid cells are considered to have a high risk of aggressivity if more than 1 mitosis/30 hpf is present. A tumor with a mitotic index between 2 and 5/50 hpf, with high cellularity and nuclear atypia, will have a malignant behavior (Figure 9).

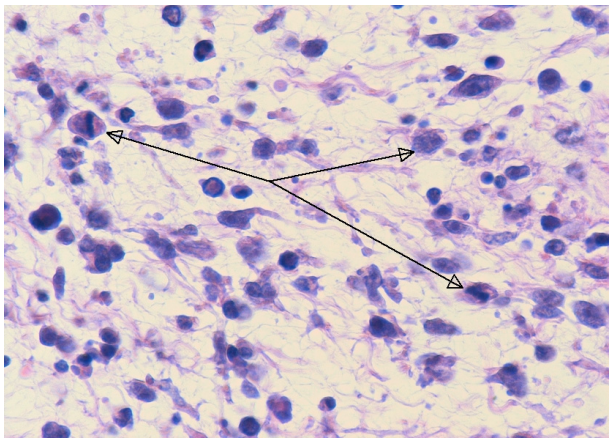

Figure 9 – ***Malignant GIST with increased mitotic activity (HE stain, ob. 40×).***

Retrospective studies have shown that the 5-year survival rate is 20% for tumors with the diameter over 10 cm and approximately 60% for GISTs with the diameter under 5 cm.

Another prognostic feature is the localization of the tumor. Several studies have demonstrated that the tumors with primary gastric localization have a better prognosis than those localized in the small intestine or rectum.

Progression of these tumors follows a characteristic evolution that includes recurrence at the level of the resection, intra-abdominal or serous dissemination and development of liver metastases. Most of the patients will develop relapse after complete surgical resection, occurring most frequently in the liver and retroperitoneally. It has to be mentioned that a relapse can also occur in low risk GISTs, even after 20 years [28]. There is reluctance to use the term **benign** to describe GISTs since this tumor may be unpredictably malignant.

Differential diagnosis

Differential diagnosis has been very much facilitated by IHC tests using a complete and specific panel of antibodies for mesenchymal tumors. Thus, tumors with smooth muscle differentiation will be taken into account: leiomyomas and leiomyosarcomas (positive for SMA and desmin, but negative for CD117 and CD34). Differential diagnosis also includes tumors with nervous differentiation: gastric schwannomas (intensely positive for S100-protein, but negative for CD117), tumors with fibrous differentiation: profound intra-abdominal fibromatosis, which affects the stomach (paucicellular, abundant in collagen fibers and CD117-negative), inflammatory gastric polyp and inflammatory myofibroblastic pseudo-tumor (both negative for CD117 and CD34). The histopathological aspects exclude the retroperitoneal undifferentiated liposarcoma, and also two mesenchymal tumors positive for c-kit: metastases of malignant melanoma (HMB45 and Melan A-positive) and angiosarcoma (CD31-positive).

The recent success in the treatment of GIST with imatinib underlines again the importance of performing these differential diagnoses with accuracy.

Treatment

Usually, GISTs treatment in resectable stages is surgery, with post-operatory surveillance. This is the conventional treatment that offers the best rate of healing in GISTs.

Unresectable and metastatic forms have an unfavorable prognostic, with an average survival rate of 12 months and weak response to usual chemotherapy used in soft tissues sarcomas. The main target of surgery is total resection of the tumor. Results are relatively good in patients with tumors of low and intermediary risk, but the relapse after complete resection is almost inevitable in tumors of high-risk. Pre-operatory histological confirmation is not necessary because of high-risk of rupture, hemorrhage or dissemination; for the same reason, the tumor must not be removed *en masse* during surgery. Because GISTs does not infiltrate the organ of origin, gastric resection or segmentary resection of the small intestine is the best therapy. Localization of the resection margins in healthy tissue should represent the main objective of the surgical intervention. Extended lymphadenectomy is not necessary as a routine procedure.

Because of the unpredictable post-operatory evolution, a follow-up using imaging methods without adjuvant therapy (that reflects in fact the inefficiency of conventional chemotherapy) for early detection of relapse (survival benefit) is necessary. Using this strategy, survival rate at one and three years in case of localized GISTs was 90% and 58% respectively. Although most of the relapses occur in the first two

years after resection, this has been seen in 80–90% of the cases in spite of complete resection with histological negative margins. Patients with GISTs relapse have an unfavorable prognostic (general survival at five years is 54%), the surgical treatment, arterial embolization or radiotherapy having little efficiency. In tumors with low mitotic index, metastasis can occur even after 10 years. Sometimes metastases affect the peritoneum, while in most soft tissue sarcomas lung metastases occur.

In metastatic and unresectable GISTs, primary surgery has been shown not to be a sufficient therapy. In advanced cases, the gold standard is a targeted therapy with tyrosine kinase inhibitors. Actually, imatinib mesylate is the first line drug administrated orally.

Imatinib mesylate is an inhibitor of different tyrosine kinases, including Bcr-Abl, c-kit and the receptor of the platelets derived growth factor (PDGF). Inhibition of Bcr-Abl explains its activity in chronic myeloid leukemia (CML). It is not yet clear in what way the inhibition of PDGF could be exploited from a clinical point of view; however, imatinib has been showed to be active in some cases of dermatofibrosarcoma protuberans by blocking PDGFs way.

It must be noticed that expression of c-kit does not necessarily mean that the tumor will respond to imatinib. The experience in using imatinib is very recent. Imatinib was approved to treat CML resistant to therapy with interferon and in February 2002 to treat GISTs.

Nowadays, imatinib mesylate is considered the standard therapy in advanced inoperable forms of GISTs. The optimal length of the treatment has not been yet established, but it is recommended to continue administration until the disease will regress. New studies concerning the role of imatinib mesylate as adjuvant or neoadjuvant therapy are under way. The phenomenon of resistance to imatinib represents the main obstacle, but progress has been recorded in the development of new kinase-dependent targets that raises new hopes in fighting the resistance to imatinib [29, 30]. In patients with multifocal GISTs in progression after imatinib new treatment modalities to control the mechanisms of molecular resistance are tested.

The multiple-target kinase inhibitor **SU11248 – sunitinib maleate** is currently tested in phase III studies. It is active in a variety of GISTs with achieved mutations that transform them in tumors resistant to imatinib. A phase II trial regarding the use of sunitinib in patients with GISTs resistant to imatinib determined a partial remission in 8% of patients and the preservation of a stationary disease aspect for a period of over six months in 37% of the patients. Nevertheless, sunitinib does not seem to be an efficient inhibitor in patients with a relapse of GISTs that show gene mutations of c-kit on the exon 11 [31].

In a period of less than 15 years, GISTs have left the anonymity and became a successful exponent of the targeted molecular therapy. Current studies tend to support the idea that these tumors do not represent a single uniform entity, but rather a family of closely related neoplasm.

New progresses are expected to define the pathways of biological signals, and that should lead into continuing the therapy success in treating GISTs. Together with the improvement of technologies and the understanding of the molecular mechanisms in cancer, transition to new therapies for the solid tumors will have to be continued after the GISTs therapy model.

References

[1] KITAMURA Y., *Gastrointestinal stromal tumors: past, present, and future*, J Gastroenterol, 2008, 43(7):499–508.

[2] NILSSON B., BÜMMING P., MEIS-KINDBLOM J. M., ODÉN A., DORTOK A., GUSTAVSSON B., SABLINSKA K., KINDBLOM L. G., *Gastrointestinal stromal tumors: the incidence, prevalence, clinical course, and prognostication in the preimatinib mesylate era – a population-based study in western Sweden*, Cancer, 2005, 103(4):821–829.

[3] TRYGGVASON G., GÍSLASON H. G., MAGNÚSSON M. K., JÓNASSON J. G., *Gastrointestinal stromal tumors in Iceland, 1990–2003: the Icelandic GIST study, a population-based incidence and pathologic risk stratification study*, Int J Cancer, 2005, 117(2):289–293.

[4] LLENAS-GARCÍA J., GUERRA-VALES J. M., MORENO A., IBARROLA C., CASTELBON F. J., FERNÁNDEZ-RUIZ M., MENEU J. C., BALLESTIN C., MORENO E., *Primary extra-gastrointestinal stromal tumors in the omentum and mesentery: a clinicopathological and immunohistochemical study*, Hepatogastroenterology, 2008, 55(84):1002–1005.

[5] REITH J. D., GOLDBLUM J. R., LYLES R. H., WEISS S. W., *Extragastrointestinal (soft tissue) stromal tumors: an analysis of 48 cases with emphasis on histologic predictors of outcome*, Mod Pathol, 2000, 13(5):577–585.

[6] MIETTINEN M., LASOTA J., SOBIN L. H., *Gastrointestinal stromal tumors of the stomach in children and young adults: a clinicopathologic, immunohistochemical, and molecular genetic study of 44 cases with long-term follow-up and review of the literature*, Am J Surg Pathol, 2005, 29(10):1373–1381.

[7] PRAKASH S., SARRAN L., SOCCI N., DEMATTEO R. P., EISENSTAT J., GRECO A. M., MAKI R. G., WEXLER L. H., LAQUAGLIA M. P., BESMER P., ANTONESCU C. R., *Gastro-intestinal stromal tumors in children and young adults: a clinicopathologic, molecular, and genomic study of 15 cases and review of the literature*, J Pediatr Hematol Oncol, 2005, 27(4):179–187.

[8] KINDBLOM L. G., REMOTTI H. E., ALDENBORG F., MEIS-KINDBLOM J. M., *Gastrointestinal pacemaker cell tumor (GIPACT): gastrointestinal stromal tumors show phenotypic characteristics of the interstitial cells of Cajal*, Am J Pathol, 1998, 152(5):1259–1269.

[9] PAULS K., MERKELBACH-BRUSE S., THAL D., BÜTTNER R., WARDELMANN E., *PDGFRalpha- and c-kit-mutated gastro-intestinal stromal tumours (GISTs) are characterized by distinctive histological and immunohistochemical features*, Histopathology, 2005, 46(2):166–175.

[10] LASOTA J., CORLESS C. L., HEINRICH M. C., DEBIEC-RYCHTER M., SCIOT R., WARDELMANN E., MERKELBACH-BRUSE S., SCHILDHAUS H. U., STEIGEN S. E., STACHURA J., WOZNIAK A., ANTONESCU C., DAUM O., MARTIN J., DEL MURO J. G., MIETTINEN M., *Clinicopathologic profile of gastrointestinal stromal tumors (GISTs) with primary KIT exon 13 or exon 17 mutations: a multicenter study on 54 cases*, Mod Pathol, 2008, 21(4):476–484.

[11] LONGLEY B. J., REGUERA M. J., MA Y., *Classes of c-KIT activating mutations: proposed mechanisms of action and implications for disease classification and therapy*, Leuk Res, 2001, 25(7):571–576.

[12] CORLESS C. L., SCHROEDER A., GRIFFITH D., TOWN A., MCGREEVEY L., HARRELL P., SHIRAGA S., BAINBRIDGE T., MORICH J., HEINRICH M. C., *PDGFRA mutations in gastrointestinal stromal tumors: frequency, spectrum and in vitro sensitivity to imatinib*, J Clin Oncol, 2005, 23(23):5357–5364.

[13] LASOTA J., STACHURA J., MIETTINEN M., *GISTs with PDGFRA exon 14 mutations represent subset of clinically favorable gastric tumors with epithelioid morphology*, Lab Invest, 2006, 86(1):94–100.
[14] ANDERSSON J., SIHTO H., MEIS-KINDBLOM J. M., JOENSUU H., NUPPONEN N., KINDBLOM L. G., *NF1-associated gastrointestinal stromal tumors have unique clinical, phenotypic, and genotypic characteristics*, Am J Surg Pathol, 2005, 29(9):1170–1176.
[15] MIETTINEN M., FETSCH J. F., SOBIN L. H., LASOTA J., *Gastrointestinal stromal tumors in patients with neurofibromatosis 1: a clinicopathologic and molecular genetic study of 45 cases*, Am J Surg Pathol, 2006, 30(1):90–96.
[16] CARNEY J. A., SWEE R. G., *Carney complex*, Am J Surg Pathol, 2002, 26(3):393.
[17] LI F. P., FLETCHER J. A., HEINRICH M. C., GARBER J. E., SALLAN S. E., CURIEL-LEWANDROWSKI C., DUENSING A., VAN DE RIJN M., SCHNIPPER L. E., DEMETRI G. D., *Familial gastrointestinal stromal tumor syndrome: phenotypic and molecular features in a kindred*, J Clin Oncol, 2005, 23(12):2735–2743.
[18] BENSIMHON D., SOYER P., BROULAND J. P., BOUDIAF M., FARGEAUDOU Y., RYMER R., *Gastrointestinal stromal tumors: role of computed tomography before and after treatment*, Gastroenterol Clin Biol, 2008, 32(1 Pt 1):91–97.
[19] MAZUR M. T., CLARK H. B., *Gastric stromal tumors. Reappraisal of histogenesis*, Am J Surg Pathol, 1983, 7(6):507–519.
[20] MIETTINEN M., SARLOMO-RIKALA M., SOBIN L. H., *Mesenchymal tumors of the muscularis mucosae of colon and rectum are benign leiomyomas that should be separated from gastrointestinal stromal tumors – a clinicopathologic and immunohistochemical study of eighty-eight cases*, Mod Pathol, 2001, 14(10):950–956.
[21] MIETTINEN M., KOPCZYNSKI J., MAKLOUF H. R., SARLOMO-RIKALA M., GYORFFY H., BURKE A., SOBIN L. H., LASOTA J., *Gastrointestinal stromal tumors, intramural leiomyomas and leiomyosarcomas in the duodenum: a clinicopathologic, immunohistochemical and molecular genetic study of 167 cases*, Am J Surg Pathol, 2003, 27(5):625–641.
[22] MIETTINEN M., MAKHLOUF H. R., SOBIN L.LASOTA J., *Gastrointestinal stromal tumors of the jejunum and ileum: a clinicopathologic, immunohistochemical, and molecular genetic study of 906 cases before imatinib with long-term follow-up*, Am J Surg Pathol, 2006, 30(4):477–489.
[23] MIETTINEN M., SOBIN L. H., LASOTA J., *Gastrointestinal stromal tumors of the stomach: a clinicopathologic, immunohistochemical, and molecular genetic study of 1765 cases with long-term follow-up*, Am J Surg Pathol, 2005, 29(1):52–68.
[24] MIETTINEN M., LASOTA J., *KIT (CD117): a review on expression in normal and neoplastic tissues, and mutations and their clinicopathologic correlation*, Appl Immunohistochem Mol Morphol, 2005, 13(3):205–220.
[25] MEDEIROS F., CORLESS C. L., DUENSING A., HORNICK J. L., OLIVEIRA A. M., HEINRICH M. C., FLETCHER J. A., FLETCHER C. D., *KIT-negative gastrointestinal stromal tumors: proof of concept and therapeutic implications*, Am J Surg Pathol, 2004, 28(7):889–894.
[26] MIETTINEN M., SHEKITKA K. M., SOBIN L. H., *Schwannomas in the colon and rectum: a clinicopathologic and immunohistochemical study of 20 cases*, Am J Surg Pathol, 2001, 25(7):846–855.
[27] FLETCHER C. D., BERMAN J. J., CORLESS C., GORSTEIN F., LASOTA J., LONGLEY B. J., MIETTINEN M., O'LEARY T. J., REMOTTI H., RUBIN B. P., SHMOOKLER B., SOBIN L. H., WEISS S. W., *Diagnosis of gastrointestinal stromal tumors: a consensus approach*, Hum Pathol, 2002, 33(5):459–465.
[28] DEMATTEO R. P., GOLD J. S., SARAN L., GÖNEN M., LIAU K. H., MAKI R. G., SINGER S., BESMER P., BRENNAN M. F., ANTONESCU C. R., *Tumor mitotic rate, size, and location independently predict recurrence after resection of primary gastrointestinal stromal tumor (GIST)*, Cancer, 2008, 112(3):608–615.
[29] ANTONESCU C. R., BESMER P., GUO T., ARKUN K., HOM G., KORYOTOWSKI B., LEVERSHA M. A., JEFFREY P. D., DESANTIS D., SINGER S., BRENNAN M. F., MAKI R. G., DEMATTEO R. P., *Acquired resistance to imatinib in gastrointestinal stromal tumor occurs through secondary gene mutation*, Clin Cancer Res, 2005, 11(11):4182–4190.
[30] CHEN L. L., SABRIPOUR M., ANDTBACKA R. H., PATEL S. R., FEIG B. W., MACAPINLAC H. A., CHOI H., WU E. F., FRAZIER M. L., BENJAMIN R. S., *Imatinib resistance in gastrointestinal stromal tumors*, Curr Oncol Rep, 2005, 7(4):293–299.
[31] LE TOURNEAU C., RAYMOND E., FAIVRE S., *Sunitinib: a novel tyrosine kinase inhibitor. A brief review of its therapeutic potential in the treatment of renal carcinoma and gastrointestinal stromal tumors (GIST)*, Ther Clin Risk Manag, 2007, 3(2):341–348.

Corresponding author
Emőke Fülöp, Assistant Professor, MD, PhD candidate, Department of Histology, University of Medicine and Pharmacy of Târgu Mureş, 38 Gheorghe Marinescu Street, 540000 Târgu Mureş, Romania; Phone +40722–365 736, e-mail: emifulop@yahoo.com

Received: January 29th, 2009

Accepted: June 15th, 2009