CASE REPORT

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Differential diagnosis of a gastric stromal tumor: case report and literature review

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Abstract

Gastrointestinal stromal tumors account for 0.1–3% of all gastrointestinal neoplasms and are characterized by features that overlap with those of other mesenchymal tumors. We expose the case of a 58-year-old male patient who complained of abdominal pain, weakness and melena. Microscopic examination of surgically resected gastric tumor revealed a neoplastic proliferation composed of spindle cells with eosinophilic cytoplasm, elongated nuclei with rounded ends, palisadic disposition and intracytoplasmic perinuclear vacuoles, low cyto-nuclear polymorphism, mild atypia and mitotic activity of 3–5/50 HPF. Some histopathological features requested differential diagnosis with schwannoma and tumors of myocytary origin, based on immunohistochemical techniques, which have established a final diagnosis of spindle cell gastric stromal tumor. We also reviewed the GIST-related literature and evaluated the possible methods of preoperative diagnosis of GISTs based on endoscopic biopsy. Proper classification of GISTs based on histopathological criteria and immunohistochemical techniques has a great prognostic and therapeutic utility. Future development of endoscopic biopsy methods will refine the management of gastrointestinal stromal tumors.

Keywords: GIST, EUS-FNA, CD117, CD34, S100, desmin.

Introduction

Gastrointestinal stromal tumors account for 0.1–3% of all gastrointestinal neoplasms and are characterized by features that overlap with those of other mesenchymal tumors. Involvement of both sexes is approximately equal and the median age of occurrence is 55–60-year-old [1, 2].

GISTs can involve any portion of digestive tract, with gastric predominance. The histogenesis of GISTs is related to the interstitial cells of Cajal or their stem-cell precursors and the pathogenesis consists mostly of c-kit or PDGFRA genes mutations [3].

GISTs have heterogeneous clinico-pathological aspects, ranging grossly from small nodules to large tumoral masses and, microscopically, exhibiting a spindle or epithelioid cell morphology or, sometimes, a pleomorphic pattern [3].

Immunohistochemical features of GISTs consists of CD117 positivity in more than 95% of cases and, with less specificity, positive reaction for CD34; GISTs are variable positive for smooth muscle markers, but positive reaction for S100 is rare [3].

This configuration of immunoreactivity is helpful to confirm the diagnosis of GIST and, supplemented with the evaluation of other markers, to differentiate it from other mesenchymal neoplasms (smooth muscle tumors, nerve sheath tumors, fibroblastic tumors), amelanotic melanoma or poorly differentiated carcinomas [3].

The main parameters of assessing the biological potential of gastrointestinal stromal neoplasms are the tumoral diameter and the mitotic count [3].

Currently, concerted efforts to establish the most viable parameters of risk stratification in GISTs are coupled with attempts to detect new methods of pre-operative diagnosis.

Materials and Methods

We expose the case of a male patient, S.I., 58-year-old, who complained of abdominal pain, weakness and melena. Patient has undergone an endoscopical examination with simultaneous biopsy from the identified gastric submucosal protrusive mass. After that, patient underwent total gastrectomy in the Surgery Department of the Emergency County Hospital of Constanța and the processing of specimen was made in the Clinical Service of Pathology, revealing particular features of the lesion.

The gastrectomy specimen was opened on the great curvature, and then it was fixed in 10% formalin. Tissue blocks were sampled from the surgical resection margins and from the tumor mass, in order to include all grossly different patterns and to be able to examine

mucosal infiltration, depth of invasion and possible vessel involvement. Lymph nodes were dissected and processed, too. Fragments of tumor were paraffin-embedded, sectioned at 5-μm and stained with Hematoxylin–Eosin (HE) and van Gieson. Immuno-histochemical analysis was based on a panel of antibodies:

- Polyclonal rabbit anti-human c-kit (CD117) (DAKO): proto-oncogene activated in GIST tumors; receptor for kit protein, a 145 kD tyrosine kinase growth factor receptor protein important for development and survival of mast cells, hematopoietic stem cells, melanocytes, germ cells, interstitial cells of Cajal; strong and diffuse cytoplasmic staining, antibodies to CD117 may be useful in the differentiation between gastrointestinal stromal tumors (GISTs) and other intra-abdominal mesenchymal tumors [1];
- Monoclonal mouse anti-human CD34 class II, clone QBEnd 10, isotype IgG1, kappa (DAKO): commonly used marker of hematopoietic progenitor cells, endothelium and dendritic interstitial cells; membranous stain; confirms diagnosis of GIST [1];
- Monoclonal mouse anti-human desmin, clone D33, isotype IgG1, kappa (DAKO): desmin is an intermediate filament present in smooth and striated muscle; this marker labels muscular neoplasms [1];
- Polyclonal rabbit anti-S100 (DAKO): the antibody is a useful tool for the identification of S100-positive neoplasms, such as malignant melanoma, chondro-blastoma, and schwannoma; additionally, it is useful for the classification of tumors of suspected histiocytic/ dendritic cell type; positive reaction in cytoplasm and nucleus [1];
- Monoclonal mouse anti-vimentin, clone Vim 3B4, isotype IgG2a, kappa (DAKO); reacts strongly with human vimentin and labels cells of mesenchymal origin [1].

Results

In the endoscopic biopsy specimen, gastric mucosa proved to be unaffected, but one fragment revealed a mesenchymal proliferation with bundles of spindle shaped cells, suggesting a preliminary diagnosis of GIST. Gross examination of the total gastrectomy specimen of 18/8 cm evidenced a submucous tumoral lesion with trinodular pattern: Φ_1=1 cm, Φ_2=2 cm and, respectively, Φ_3=3 cm; white-grayish section surface revealed the presence of empty small slits; the consistency was variable (moderate/firm) and the friability was relative. Apparently, the tumor did not infiltrate the mucosa and serosa was not retracted. The surgical resection borders were located at 5 cm proximally and 7 cm distally to the tumor and were macroscopically uninvolved (Figure 1).

Microscopy revealed a neoplastic proliferation composed of spindle cells with eosinophilic cytoplasm, elongated nuclei with rounded ends (Figure 2), palisadic disposition (Figures 3 and 6) and intracytoplasmic peri-nuclear vacuoles (Figure 4); cellular arrangement is in short fascicles that intersect haphazardly; we remarked hypercellular areas (Figures 5 and 6), low cyto-nuclear polymorphism, mild atypia and mitotic activity of 3–5/50 HPF (Figure 7).

Throughout the tumor, fibro-hyaline septa were identified, admixed with myxoid areas and well-developed vessels. Foci of tumoral necrosis were absent. The cellular proliferation did not invade mucosa (Figure 8); it remained separated by fibrosis with hyalinization and does not extend outside the serosal surface.

Suprajacent mucosa showed atrophy and areas of hemorrhagic infiltration. The surgical resection borders were free of tumor proliferation. Lymph nodes were not involved.

Histopathological aspects pleaded for the diagnosis of spindle cells GIST [2] of histological grade II (Table 1).

Table 1 – ***Histological grade of GISTs***

Grade	Mitotic activity	Cellularity	Atypia	Necrosis
I	<3/50 HPF	Mild-moderate	Absent	Absent
II	3–5/50 HPF	Moderate	Mild	Absent
III	>6/50 HPF	Intense	Moderate	Focal
IV	>6/50 HPF	Intense	Severe	Intense, diffuse

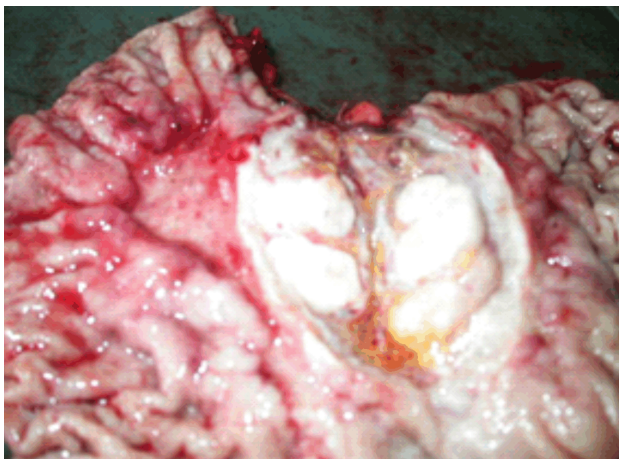

Figure 1 – ***Macroscopic aspect.***

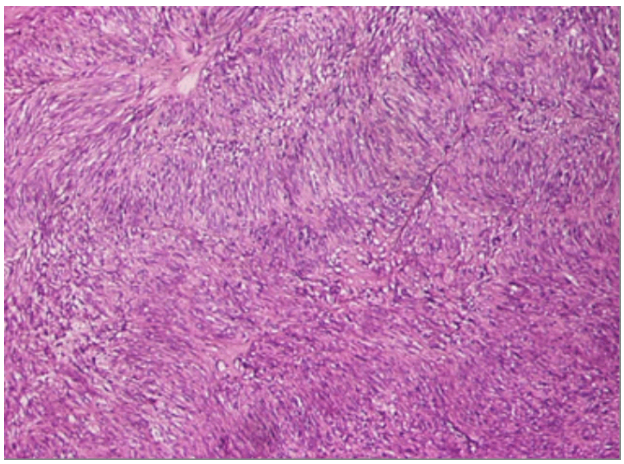

Figure 2 – ***Spindle cells with fasciculated disposition (HE stain, ×100).***

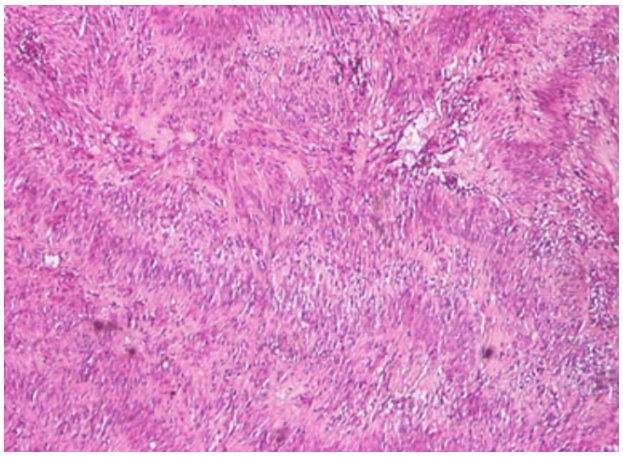

Figure 3 – ***Palisadic disposition of neoplastic cells (HE stain, ×100).***

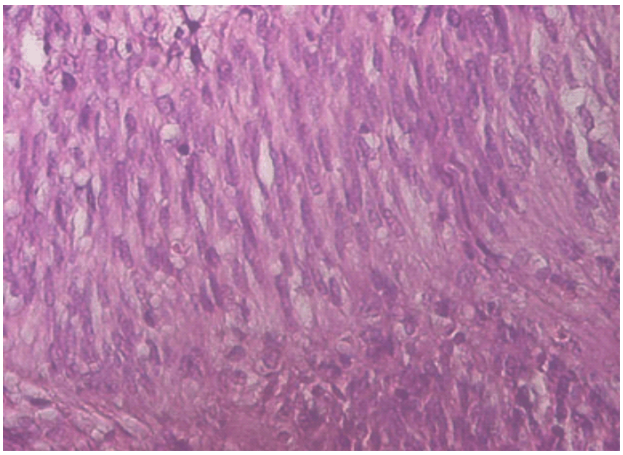

Figure 4 – ***Perinuclear vacuoles (HE stain, ×200).***

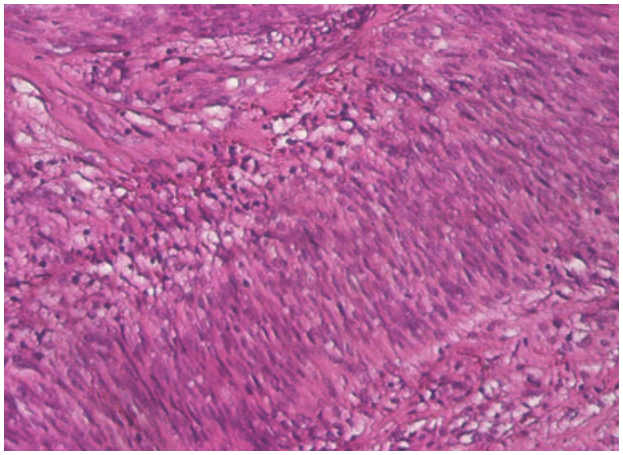

Figure 5 – ***Hypercellular areas (HE stain, ×200).***

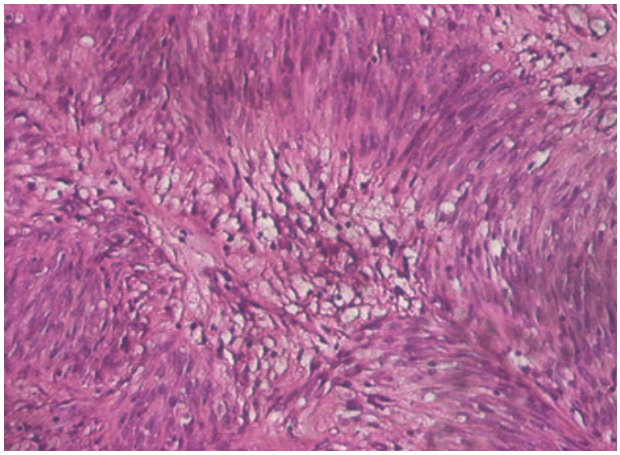

Figure 6 – ***Hypercellular areas with palisadic disposition (HE stain, ×200).***

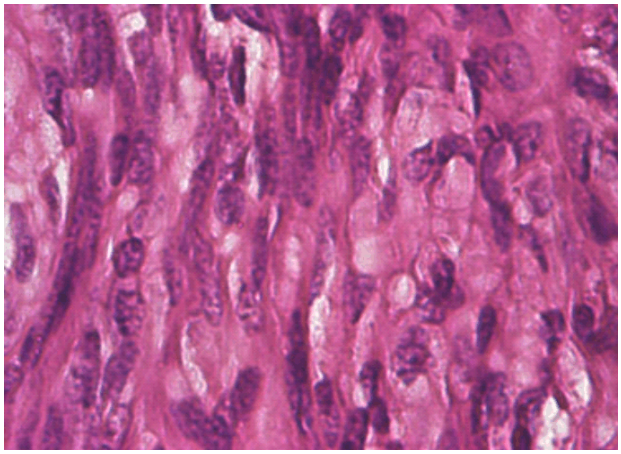

Figure 7 – ***Aspect of mitoses (HE stain, ×400).***

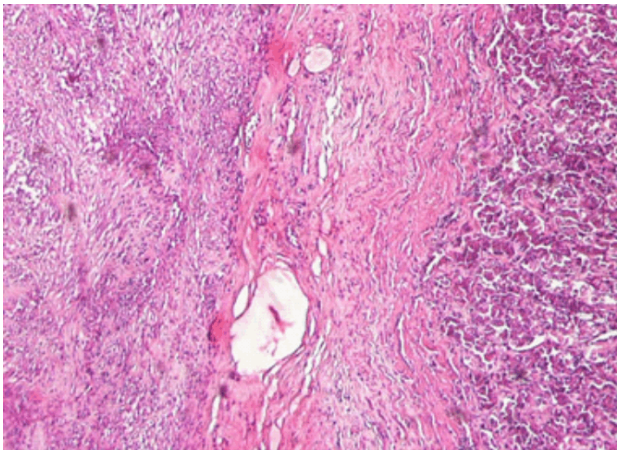

Figure 8 – ***The relationship between gastric mucosa and tumoral proliferation (HE stain, ×40).***

Palisadic arrangement of nuclei required diagnosis of exclusion with schwannoma. On the other hand, fasciculated character of dense cellular population with rounded edge nuclei suggested the possible myocytary origin of neoplastic population and imposed differential diagnosis with leiomyosarcoma. These segregations were made on immunohistochemical base.

The use of monoclonal antibodies revealed following features of tumoral proliferation:

- CD117: intense positive reaction (+++) (Figures 9 and 10);
- CD34: moderate positive reaction (++) (Figure 11);
- Vimentin: moderate positive reaction (++) (Figure 12);
- S100: weak focal positive reaction (+) (Figure 13);
- Desmin: negative reaction (-) (Figure 14).

Immunohistochemical profile confirmed the diagnosis of gastric stromal tumor. The presence of low S100 immunoreactivity represented an unfavorable prognosis factor, especially for GIST with gastric location.

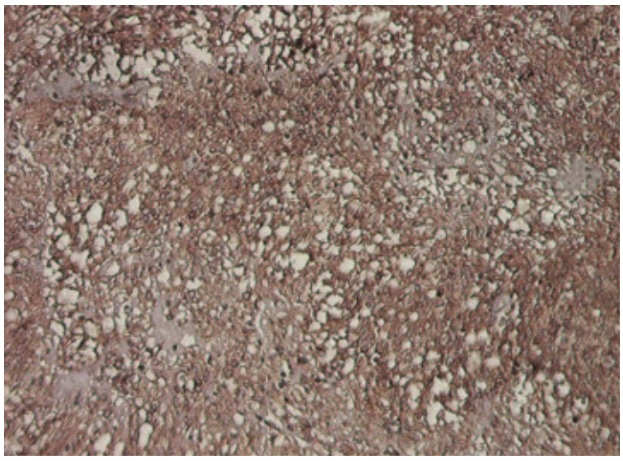

Figure 9 – ***Positive reaction for CD117 in neoplastic population (×100).***

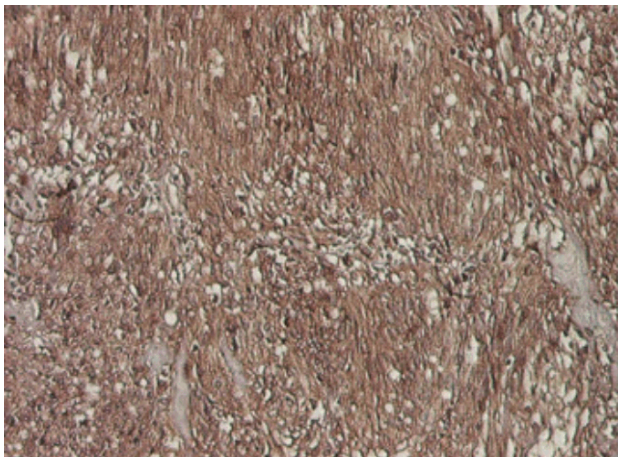

Figure 10 – ***Positive reaction for CD117 in neoplastic cells (×200).***

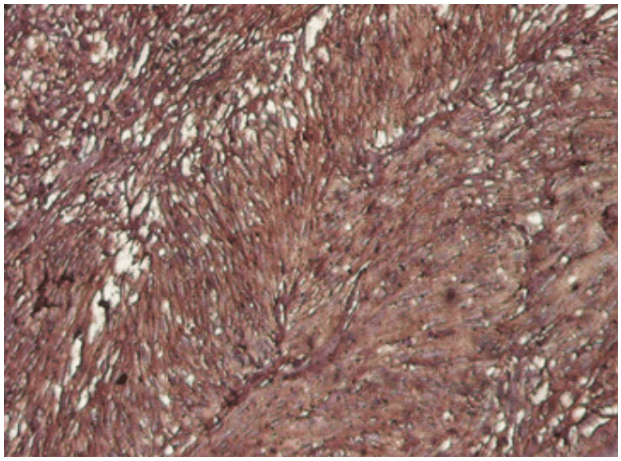

Figure 11 – ***Positive reaction for CD34 in neoplastic population (×200).***

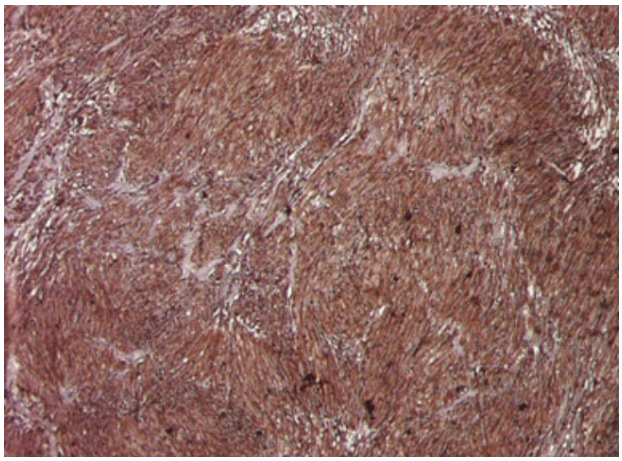

Figure 12 – ***Positive reaction for vimentin in tumoral cells (×200).***

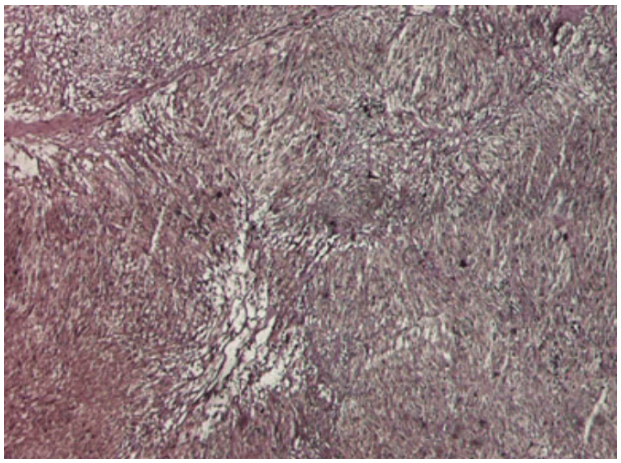

Figure 13 – ***Weak focal positive reaction for S100 in tumoral population (×200).***

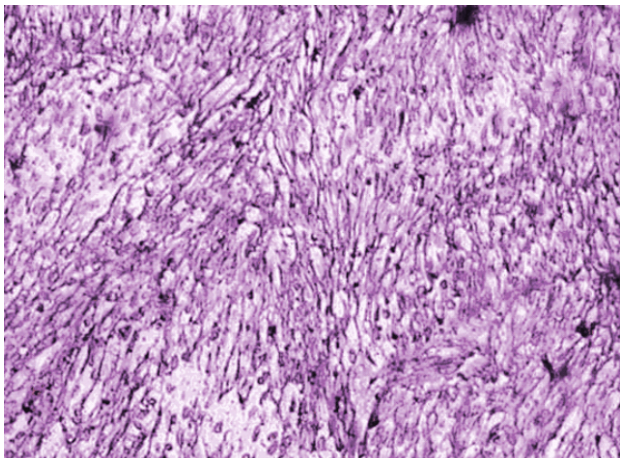

Figure 14 – ***Negative reaction for desmin in tumoral population (×400).***

Discussion

Overview

Gastrointestinal stromal tumors (GISTs) are rare mesenchymal tumors that develop in the gastrointestinal tract or, rarely, in the abdominal cavity, unrelated to the digestive wall. They represent 0.1–3% of all gastrointestinal tumors and 5–6% of sarcomas. Usually, GISTs appear between the fourth and seventh decade of life and affect both sexes in relative equal proportions.

For a long time, it was considered that tumors belonging to GISTs group where those of smooth muscle origin, tumors of nervous origin and undifferentiated tumors. Identification of c-kit gene mutations and setting of the immunophenotype demonstrated that GISTs constitutes an entity different from tumors with smooth muscle and nervous origin [3].

GISTs originate from interstitial cells of Cajal (ICC), from less differentiated stem cell or from

precursor cell of ICC. Cajal interstitial cells form a complex cellular network in the muscle layer of the digestive tract, representing the pacemaker of peristalsis. Expression of c-kit proto-oncogene, located on chromosome 4q11–21, is essential for the development of ICC and for the initiation of the slow waves caused by them. Identification of c-kit using CD117 is a marker for ICC.

Mutations of the c-kit are probably the *primum movens* in the development of GISTs. They have been identified in more than 50% of GISTs, most commonly in the exon 11, that encode the juxtamembranary domain. They consist in deletions and point mutations that result in hyperfunction with permanent activation of the receptor. The rarest mutations involve the exons 9 and 13 that encode the extracellular and enzymatic domains. Molecular genetic studies have shown that mutations in the c-kit exon 11 occur most frequently in GISTs with malignant clinico-biological behavior and morphology. Identification of the enzymatic and regulatory mutations, allowed *in vitro* demonstration that GISTs with mutations in the regulatory region respond better to ST1-571 (Gleevec) therapy than GISTs with mutations in the enzymatic region. A small percentage of GISTs presents c-kit mutations that cannot be detected by conventional methods; in this situation, probably, the c-kit kinase activation is produced by non-mutational mechanisms. In familial GISTs, mutations in exons 11 and 13 were identified. Typically, these patients develop diffuse hyperplasia of Cajal cells, considered preneoplastic lesions [3].

C-kit mutations have not been demonstrated in leiomyomas and leiomyosarcomas, which confirms the idea that GISTs represent a different entity from them.

Concerning the location of GISTs, 60–70% of all cases are located in the stomach, 20–30% in the small bowel and 10% or less in the esophagus, colon and rectum [3].

Macroscopic description

Gross patterns of GISTs reveal a variety of aspects: solid subserosal, intramural or polypoid intraluminal masses, with diameter ranging between 1–20 cm; they are generally well defined, but without an own capsule; the section surface may have a gray or pinkish color, with possible areas of cystic change, hemorrhage, necrosis. Central necrosis development in large tumors leads to a diverticulum-like appearance with the external tumor communicating with the lumen by a fistula tract. Some GISTs have an asymmetric hourglass-like pattern with a smaller internal and a larger external component [3].

Histopathological variants of gastric GISTs

Histologic patterns of gastric GISTs recognize eight subtypes: four of them consist of an epithelioid cellular population and the other four are composed of spindle cells.

Sclerosing epithelioid cell GISTs feature sheets of polyhedral cells with a syncytial disposition in a collagenous stroma, interspersed with multinucleated cells; the mitotic rate is low.

Dyscohesive epithelioid variant is characterized by polygonal cells surrounded by a clear halo; neoplastic cells have distinctive borders and mild nuclear pleomorphism.

Hypercellular epithelioid form consists of a rich neoplastic population with low mitotic activity.

Sarcomatous epithelioid cell type of GISTs represents highly cellular tumor with high mitotic rate.

Sclerosing spindle cell GISTs are characterized by hypocellularity, neoplastic cells being distributed into a collagenous stroma with focal calcification.

Palisading vacuolated type of GISTs represents the most common histopathological form of gastric stromal neoplasms with spindle cells and shows schwannoma-like nuclear palisading, distinctive perinuclear vacuolation and low mitotic activity.

Hypercellular spindle cell variant of GISTs is composed of a dense population without important atypia and a low mitotic count.

Sarcomatous spindle cell form of GISTs shows karyomegaly, nuclear hyperchromatism and an intense mitotic activity [3].

Immunohistochemical features

CD117 expression is defining this group of tumors; it was observed in most GISTs and is consistent with the origin, histological pattern and biological evolution. CD117 labeling of the GIST cells may be intense and diffuse cytoplasmic or may take the form of intracytoplasmic drops ("Golgi appearance"). These patterns of positive reaction reflect different types of c-kit mutations. Proportion of CD117 positive cells in GISTs varies between 5–90%; this information is useful in the interpretation of biopsies taken from tumors suggestive for GISTs.

Tumors with morphological aspect of GISTs, but CD117 negative, are called GIST-like [3].

CD117 can be expressed in other tumor types: dermatofibrosarcoma protuberans, synovial sarcoma, rhabdomyosarcoma, large cell anaplastic lymphoma, glioma, dysgerminoma, malignant melanoma, AML.

Another positive immunohistochemical marker of GIST is CD34, a protein normally expressed in hematopoietic precursor cells and some interstitial Cajal cells. CD34 is positive in the cytoplasmic compartment, because it is stored intracellularly and it is rapidly translocated to the plasma membrane in response to extracellular signals [3].

Approximately 60–70% of GIST are positive for CD34, but this proportion varies according to tumor location.

CD34 expression is intense in 85% of gastric GIST, but appears in only 50% of GIST of the small intestine [4, 5]. In the uncommon locations of GISTs, Miettinen M *et al.* (2000) [6] reported CD34 positivity in 100% of esophageal GIST, 65% of colonic GIST, 96% of rectal GIST and 65% of extraGIST. Some solitary fibrous tumors or schwannomas may be positive for CD34, representing some of the tumors that must be differentiated from GISTs.

In order to identify the presence of smooth muscle cell or neural differentiation, markers as smooth muscle

actin (SMA), desmin or S100, respectively, are used. A small percentage of GISTs may show positivity for SMA, S100 and desmin, observation without diagnostic significance if the tumors are CD117 positive. If CD117 is negative, then diagnosis is that of tumor with smooth muscle fiber origin (leiomyoma and leiomyosarcoma), if it is positive for SMA and desmin or tumor of neural origin (schwannoma or others), if it is positive for S100.

Vimentin is another immunohistochemical marker that exhibits positive reaction in GISTs, but the wide expression of vimentin in many histopathological entities determines this information to be of little diagnostic significance.

So, typical GISTs tumors are characterized by following immunohistochemical profile: CD117+ (95% of cases), CD34+ (60–70% of cases) and vimentin almost constantly. Approximately 20–40% of GIST have focal reaction for SMA, 2–4% present response for desmin and 5% for S100 [6].

CD117 negative GISTs are uncommon, but about 5% of cases of GISTs are not positive for c-kit [7, 8]. These cases are real challenges for the pathologist, that in such situations must assess the results of other markers, as well as cellular characteristics, in order to determine the most probable diagnosis. Additional markers that have been identified in recent years are helpful in such cases: PKC-θ, PDGFRA and DOG1. Protein kinase C-theta (PKC-θ) is a highly expressed marker in CD117 negative GISTs [9]. Mutation of the PDGFRA receptor, another tyrosine kinase receptor could be related to oncogenesis in these cases [10]. Another marker known as DOG1 ("discovered on GIST1") is positive in GIST [11]. Positive reactions of these markers help to distinguish CD117 negative GISTs from other types of tumors, which is important for choosing a correct diagnosis and treatment protocol.

There is a variety of gastrointestinal stromal tumors with neural differentiation of autonomous nerves type – gastrointestinal GANT. Originally designated as plexomas or plexosarcomas, they have morphological aspects of cellular structures resembling enteric autonomic plexus. Typically, GANT consist of epithelioid or spindle cells have a low histological grade, express S100, NSE, synaptophysin, vimentin and are CD34 negative [3].

Differential diagnosis of gastric stromal tumors

Achieving a rigorous differential diagnosis of gastric stromal tumors from other mesenchymal tumors of stomach requires analysis of all their characteristics.

Differentiation of gastric stromal tumor from a smooth muscle tumor needs an in-depth study of the features of the later. In stomach, smooth muscle neoplasms are infrequent. Leiomyomas occur in young patients, can be located intramural or intraluminal (as polypoid masses arising from muscularis mucosae) and are composed of mature, focally atypical smooth muscle cells. A peculiar type of leiomyoma is the uterine-type, histologically similar with that occurring in genital location. Gastric uterine-type leiomyoma is imunohisto-chemically positive for SMA, desmin, estrogen and progesterone receptors. Segregation of these neoplasms from gastric stromal tumors is significant for management, because the former require a more conservative approach [3].

Primary gastric leiomyosarcomas are extremely rare; they can form polypoid lesions that microscopically are similar with those peripherally localized and immuno-histochemically exhibit positive reactions for SMA and desmin and negativity for CD117. These neoplasms have a better prognosis than stromal tumors with similar diameter and mitotic count [3].

Gastric schwannomas occur in 60–70% of cases in this location and affect elderly. Grossly, they are small tumors (diameter <5 cm) with nodular shape and intramural disposition. Histopathologically, they are composed of spindle cells with focal atypia and low mitotic activity (<5/50 HPF), surrounded by a lymphoid border. The architectural pattern is fasciculated or microtrabecular, intermingled with fibrovascular septa. A rare variant consists of epithelioid cells and exhibits a polypoid appearance. Immunohistochemically, gastric schwannomas are S100, vimentin and GFAP (glial fibrillary acidic protein) positive; CD34, CD117, desmin and SMA negative [3].

Other clinico-pathological mimickers of gastric stromal tumors are: metastatic amelanotic melanoma (S100 and HMB45 positive; CD117 focally positive or negative), clear cell sarcoma (S100 positive and t(12;22) translocation), desmoid tumor (nuclear beta-catenin positivity), inflammatory myofibroblastic tumor (vimentin, SMA, and ALK1/p80 positive; CD117, S100 and CD34 negative), inflammatory fibroid polyp (Vimentin, CD34, SMA and HHF-35 positive; CD117 and S100 negative) and pleomorphic, highly mitotically active sarcomatoid carcinoma (CEA, EMA, cytokeratin positive; CD117 and CD34 negative) [3].

Evolution of GISTs. Particular criteria for gastric stromal tumors

Many authors have reported that the evolution and prognosis of these tumors varies according to tumoral grade, based on particular features. Evaluation of biologic potential of GISTs is based on the assessment of following criteria: tumor size, cellularity, involvement of mucosa, nuclear atypia, mitotic activity, stromal aspect. Poor prognostic factors comprise large tumoral diameter (>7 cm), high cellularity, mucosal invasion, high nuclear grade, presence of more than 5 mitoses/50 HPF, myxoid stroma [3].

These features are grouped in minor and major criteria that determine the biological behavior of GISTs (Table 2) [12].

Table 2 – ***Criteria for evaluation of biological behavior of GISTs (adapted from Bucher P et al., 2004 [12])***

Minor criteria	
Tumor size [cm]	≥5
Mitotic index	≥5 mitoses/50 HPF
Presence of necrosis	
Infiltration of adjacent structures (i.e. mucosa or serosa)	
MiB1 index [%]	≥10

Major criteria
Presence of lymph node invasion
Presence of GIST metastases

Low malignant potential GISTs are considered to be those stromal neoplasms with fewer than four minor criteria. High malignant potential GISTs are those with four or five minor criteria or one major criterion.

Easier to be applied by the pathologist is the two criteria-scales, elaborated by the consensus approach supported by the National Institute of Health adapted from Fletcher CD *et al.*, consisting in two parameters of evaluation: tumor size and mitotic count (Table 3) [13–17].

Table 3 – ***Two criteria-scale table for histo-pathological evaluation of biologic potential of GISTs (adapted from Fletcher CD et al., 2002 [13])***

Risk of aggressive behavior	Tumor size [cm]	Mitotic count
Very low risk	<2	<5/50 HPF
Low risk	2–5	<5/50 HPF
Intermediate risk	<5	6–10/50 HPF
	5–10	<5/50 HPF
High risk	>5	>5/50 HPF
	>10	Any mitotic rate
	Any size	>10/50 HPF

The application of these criteria must be done differently for stromal tumors of stomach and small bowel, because gastric and intestinal neoplasms with similar features have distinct biologic potentials, more favorable for gastric tumors.

Stratification of risk in case of gastric and intestinal stromal tumors shows the differences (Table 4) [18].

Table 4 – ***Stratification of risk in gastric and intestinal stromal tumors (adapted from Miettinen M et al., 2006 [18])***

Risk of aggressive behavior		Tumor size [cm]	Mitotic count
Stomach	***Small bowel***		
None	None	<2	<5/50 HPF
Very low	Low	2–5	<5/50 HPF
Low	Moderate	5–10	<5/50 HPF
Moderate	High	>10	<5/50 HPF
None	High	<2	>5/50 HPF
Moderate	High	2–5	>5/50 HPF
High	High	5–10	>5/50 HPF
High	High	>10	>5/50 HPF

In addition to these criteria, of prognosis importance is the use of markers for proliferative activity (Ki67) and for the loss of p16 cell cycle regulator, both of them indicating an aggressive behavior [3].

Analyzing all the presented elements, our case fits in the diagnosis of palisading vacuolated type of spindle cell gastric stromal tumor of histological grade II. Dimensions of the neoplasm, the presence of foci of marked cellularity and myxoid areas sustained the possible malignant behavior of the lesion, but with low potential, considering the gastric location of it.

Endoscopic biopsy of gastric stromal tumors: pros and cons

Our case exhibited concordance between the microscopic aspect of the endoscopic bioptic sample and the histopathological characteristics evidenced on the surgical resection specimen. This represents a rare situation, because the submucosal location of GISTs determines the difficulty of the establishment of the correct pre-operative diagnosis. In many cases, the submucosal GISTs mimics adenocarcinoma during endoscopical examination, due to irregular aspect of mucosa that covers the stromal neoplasm, fact that raises the necessity of tumoral sampling for the accurate pre-operative diagnosis. Unfortunately, only a small number of GISTs evidence on bioptic specimens relevant histopathological criteria for diagnosis of stromal tumor, due to deep location of them. In order to obtain larger pieces and to sample deeper areas, advanced methods like use of jumbo biopsy forceps and "bite-on-bite" technique are used. In a recent study, Cantor MJ *et al.* [19] compared these two methods and their usefulness in endoscopic removal of small submucosal tumors and found a significant difference (p<0.0001) in the effectiveness of correct diagnosis of subepithelial tumors. Supplementary application of immunohistochemical methods (CD117) on bioptic specimens bring additional information to document the diagnosis of GIST. However, the information provided by biopsy specimen is insufficient for grading and for prognostic evaluation, but infiltration of lamina propria and mitotic activity correlated with tumoral diameter could be useful. Campbell F *et al.* [20] have noticed that evidence of lamina propria invasion on bioptic specimen is highly suggestive for malignant behavior. Debnath S *et al.* [21] think that proper endoscopy with larger biopsies that include deeper proliferative elements, may be helpful in the preoperative diagnosis of submucosal GISTs. On the other hand, Miettinen M and Lasota J [22] consider that endoscopic biopsy is often successful in diagnosing an ulcerated GIST, but tumors that have not ulcerated are usually inaccessible by endoscopic biopsy. In addition, Akyüz U *et al.* [23] agree this idea and accept that endoscopic biopsy is unnecessary for preoperative diagnosis of GIST, because, anyway, surgical resection of GISTs should be performed. Also, the risk of bleeding after bioptic procedure should be considered.

Currently, there is a consensus regarding the best method in the pre-operative diagnostic of GIST: endoscopic ultrasonography with fine needle biopsy (EUS-FNA). Its importance consists in the applicability of the method in many directions: segregation of GIST from other neoplasms with similar endoscopic features (leiomyoma, schwannoma, carcinoid, lymphoma, ectopic pancreas, metastases) and effectuation of immunohistochemical techniques (CD117) on sampled cells, in order to confirm the diagnosis of GIST. Akahoshi K *et al.* [24] say that this procedure has a high diagnostic accuracy and a great importance for the further surgical and oncological management of the lesion. They consider that extensive use of EUS-FNA in the diagnostic algorithm of GISTs would considerably improve the prognosis of this disease, by stratification of cases and application of the appropriate therapy. However, the risks of EUS-FNA should be considered: peritoneal spreading of neoplastic cells or tumor

rupture. Many authors recommend the performance of this procedure in all digestive tract submucosal tumors larger than 1 cm or in patients not suitable for surgery [24, 25].

Conclusions

Proper classification of GISTs based on histopathological criteria and immunohistochemical techniques has a great prognostic and therapeutic utility. Future development of endoscopic biopsy methods will refine the management of gastrointestinal stromal tumors.

References

[1] Fletcher CDM, *Diagnostic histopathology of tumors*, 3rd edition, Churchill Livingstone, 2007.

[2] Odze RD, Golblum JR, Crawford JM, *Surgical pathology of the GI tract, liver, biliary tract, and pancreas*, Elsevier, 2004.

[3] Miettinen M, Lasota J, *Gastrointestinal stromal tumors: review on morphology, molecular pathology, prognosis, and differential diagnosis*, Arch Pathol Lab Med, 2006, 130(10):1466–1478.

[4] Hasegawa T, Matsuno Y, Shimoda T, Hirohashi S, *Gastrointestinal stromal tumor: consistent CD117 immunostaining for diagnosis, and prognostic classification based on tumor size and MIB-1 grade*, Hum Pathol, 2002, 33(6):669–676.

[5] Rudolph P, Gloeckner K, Parwaresch R, Harms D, Schmidt D, *Immunophenotype, proliferation, DNA ploidy, and biological behavior of gastrointestinal stromal tumors: a multivariate clinicopathologic study*, Hum Pathol, 1998, 29(8):791–800.

[6] Miettinen M, Sobin LH, Sarlomo-Rikala M, *Immunohistochemical spectrum of GISTs at different sites and their differential diagnosis with a reference to CD117 (KIT)*, Mod Pathol, 2000, 13(10):1134–1142.

[7] Orosz Z, Tornóczky T, Sápi Z, *Gastrointestinal stromal tumors: a clinicopathologic and immunohistochemical study of 136 cases*, Pathol Oncol Res, 2005, 11(1):11–21.

[8] Tzen CY, Mau BL, *Analysis of CD117-negative gastrointestinal stromal tumors*, World J Gastroenterol, 2005, 11(7):1052–1055.

[9] Blay P, Astudillo A, Buesa JM, Campo E, Abad M, García-García J, Miquel R, Marco V, Sierra M, Losa R, Lacave A, Braña A, Balbín M, Freije JM, *Protein kinase C theta is highly expressed in gastrointestinal stromal tumors but not in other mesenchymal neoplasias*, Clin Cancer Res, 2004, 10(12 Pt 1):4089–4095.

[10] Wasag B, Debiec-Rychter M, Pauwels P, Stul M, Vranckx H, Oosterom AV, Hagemeijer A, Sciot R, *Differential expression of KIT/PDGFRA mutant isoforms in epithelioid and mixed variants of gastrointestinal stromal tumors depends predominantly on the tumor site*, Mod Pathol, 2004, 17(8):889–894.

[11] West RB, Corless CL, Chen X, Rubin BP, Subramanian S, Montgomery K, Zhu S, Ball CA, Nielsen TO, Patel R, Goldblum JR, Brown PO, Heinrich MC, van de Rijn M, *The novel marker, DOG1, is expressed ubiquitously in gastrointestinal stromal tumors irrespective of KIT or PDGFRA mutation status*, Am J Pathol, 2004, 165(1):107–113.

[12] Bucher P, Taylor S, Villiger P, Morel P, Brundler MA, *Are there any prognostic factors for small intestinal stromal tumors?* Am J Surg, 2004, 187(6):761–766.

[13] Fletcher CD, Berman JJ, Corless C, Gorstein F, Lasota J, Longley BJ, Miettinen M, O'Leary TJ, Remotti H, Rubin BP, Shmookler B, Sobin LH, Weiss SW, *Diagnosis of gastrointestinal stromal tumors: a consensus approach*, Hum Pathol, 2002, 33(5):459–465.

[14] Franquemont DW, *Differentiation and risk assessment of gastrointestinal stromal tumors*, Am J Clin Pathol, 1995, 103(1):41–47.

[15] Ma CK, Amin MB, Kintanar E, Linden MD, Zarbo RJ, *Immunohistologic characterization of gastrointestinal stromal tumors: a study of 82 cases compared with 11 cases of leiomyomas*, Mod Pathol, 1993, 6(2):139–144.

[16] Franquemont DW, Frierson HF JR, *Proliferating cell nuclear antigen immunoreactivity and prognosis of gastrointestinal stromal tumors*, Mod Pathol, 1995, 8(5):473–477.

[17] Miettinen M, El-Rifai W, H L Sobin L, Lasota J, *Evaluation of malignancy and prognosis of gastrointestinal stromal tumors: a review*, Hum Pathol, 2002, 33(5):478–483.

[18] Miettinen M, Makhlouf H, Sobin LH, 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.

[19] Cantor MJ, Davila RE, Faigel DO, *Yield of tissue sampling for subepithelial lesions evaluated by EUS: a comparison between forceps biopsies and endoscopic submucosal resection*, Gastrointest Endosc, 2006, 64(1):29–34.

[20] Campbell F, Bogomoletz WV, Williams GT, Tumors of the esophagus and the stomach. In: Fletcher CDM (ed), *Diagnostic histopathology of tumours*, vol. 1, Churchill Livingstone, Philadelphia, 2002, 313–367.

[21] Debnath S, Misra V, Misra SP, Singh PA, Dwivedi M, *Preoperative diagnosis of gastrointestinal stromal tumour of stomach by endoscopic biopsy: report of two cases*, J Clin Diagn Res [serial online], 2008, 2(2):747–750.

[22] Miettinen M, Lasota J, *Gastrointestinal stromal tumors: pathology and prognosis at different sites*, Semin Diagn Pathol, 2006, 23(2):70–83.

[23] Akyüz U, Erzin Y, Cengiz C, *Diagnosis of gastrointestinal stromal tumors with double-balloon enteroscopy*, Turk J Gastroenterol, 2010, 21(1):39–41.

[24] Akahoshi K, Oya M, *Gastrointestinal stromal tumor of the stomach: how to manage?* World J Gastrointest Endosc, 2010, 2(8):271–277.

[25] Smyła Z, Kurek J, Zaniewski M, Piekorz P, Sandelewski A, Majewski E, Kosteczki J, Antosz Z, *The diagnostic difficulties of gastrointestinal stromal tumours (GIST)*, Ann Acad Med Siles, 2005, 59(3):182–185.

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