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Histopathological and immunohistochemical features of gastrointestinal stromal tumors

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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 cells, seldom of epithelioid cells or both spindle and epithelioid cells – and on immunohistochemical arguments – expression of CD117 usually associated with CD34 expression. The evaluation of the prognosis is essential and based on a simple algorithm using two prognostic parameters, tumor size and mitotic index. The aim of this paper is a complex histopathological assessment, using both classic and modern (immunohistochemistry) techniques, of the GISTs comprised in the study. GISTs occur mainly in older adults (median age 60–69 years), anywhere along the gastrointestinal tract but also retroperitoneal. Most of them were nodular (75%), tumor necrosis and mucosal ulceration being the most frequent encountered secondary alterations; these modifications proved to be significantly correlated with large tumor size and high malignancy. Immunohistochemical evaluation revealed that 77 (97%) cases of GISTs presented a positive reaction for CD117, 50 (63%) cases were positive for CD34, 19 (24%) were positive for SMA and only 10 (13%) were positive for S100. Immunohistochemical evaluation remains an important tool of pathology in the diagnosis of GISTs, in the differential diagnosis from other gastrointestinal mesenchymal tumors and represents the gold standard for diagnosis of these tumors and an eligibility criterion for imatinib therapy.

Keywords: gastrointestinal stromal tumors, immunohistochemistry, CD117, prognostic criteria.

Introduction

Immunohistochemical and molecular studies targeted at gastrointestinal tumors with mesenchymal origin have proved that a large number of these tumors arise from a specific category of cells, the interstitial cells of Cajal, and are called "gastrointestinal stromal tumors" (GISTs). In a period of less than ten years, GISTs have evolved from relative anonymity to a successful contender to targeted molecular therapies [1]. At present, FDA has established imatinib therapy as the first line of treatment in metastatic, non-resectable or sub-optimally resected GISTs [2–4]. Given that these tumors have a tendency for multiple recidivisms over their evolution, there are several 3rd phase studies that prove the utility of the imatinib therapy in GISTs with a high degree of malignancy [5, 6].

Materials and Methods

We have carried out both a retrospective study based upon pathology reports and a microscopic and immunohistochemical (IHC) reassessment of the cases.

The study group includes 79 cases of GIST, resulted from reassessment of 51 cases previously diagnosed as GIST, 51 cases of smooth muscle tumors (leiomyoma, leiomyosarcoma) and 16 cases of peripheral nerve sheath tumors (schwannoma, neurofibroma). Cases originate from the Pathology Laboratory, Târgu Mureş, from the period 2002–2008.

IHC staining was performed upon 0.3–0.4 μm thick sections, on Polysine™ slides. Antigen retrieval was achieved by using the HIER (Heat Induced Epitope Retrieval) method. We selected the primary antibodies based upon their sensitivity as retrieved from the literature: CD117/c-kit (DAKO, 1:500), CD34 (Class II, clone QBEnd-10, DAKO, 1:50), SMA Ab-1 (LabVision, 1:200), S100 (DAKO, 1:400). The detection system used was Ultra Vision LP Detection, System AP Polymer (LabVision), the chromogen used was 3,3'-diamino-benzidine and Hematoxylin was used for nuclear counterstaining. IHC staining was performed in the Department of Immunohistochemistry of the Pathology Laboratory, Târgu Mureş, and in the Laboratory of Immunohistochemistry of the Department of Histology from the University of Medicine and Pharmacy of Târgu Mureş. Only the initials of the patients' names were used for identification, thus ensuring data confidentiality.

In order to classify GISTs according to their degree of malignancy, we used the most recommended and widely accepted system, devised by an international consensus on GIST diagnosis (Table 1) [7].

These data were included in a study sheet specially conceived for data collection and coded into a dictionary of variables for subsequent processing, which comprised both a descriptive and a comparative analysis. All statistic analyses were performed with the demo version of the GraphPad InStat software and the 17th version of SPSS program. Data were analyzed with the help of test χ^2 and Fisher's Exact Test. Differences were considered as statistical significant in cases with the value of p parameter less than 0.05.

Table 1 – ***Criteria for GISTs malignancy degree classification according to the 2002 International Consensus***

Degree of malignancy	Tumor size	Mitotic index
Very low	<2 cm	<5/50 HPF
Low	2–5 cm	<5/50 HPF
Intermediate	<5 cm 5–10 cm	6–10/50 HPF <5/50 HPF
High	>5 cm >10 cm any size	>5/50 HPF indifferent >10/50 HPF

Results

Establishment of study group

After interpretation of IHC reactions, into those three types of mesenchymal tumors, we obtained the following immunohistochemical profiles:

▪ Tumors with CD117+, CD34±, SMA± and S100±: in 45 cases of GIST, 26 cases of smooth muscle tumors and six cases of neural tumors; so, in these cases the proposed diagnoses was certainly that of GIST.

▪ Tumors with CD117+, CD34±, SMA± and S100±: observed in two cases of GIST, cases in which the diagnoses of GIST was suspected. To support this diagnostic further investigations with other antibodies (vimentin, desmin, NSE, CK) are required, and based on the results the diagnostic of GIST was proposed.

▪ Tumors with CD117-, CD34-, SMA+ and S100-: observed in three cases of GIST and 25 cases of smooth muscle tumors, in that was proposed the diagnosis of tumor of muscular origin.

▪ Tumors with CD117-, CD34-, SMA- and S100+: observed in one case of GIST and 10 cases of neural tumors, in which the diagnosis of peripheral nerve sheath tumors was proposed.

GISTs general features

Concerning the GISTs age distribution, we noticed that persons over 50-year-old were the most affected, with a peak of incidence in the 60–69-year-old group (Figure 1).

According to our descriptive analysis, the mean patient age was 59.94 years, with the youngest patient being 30-year-old and the oldest 95-year-old. Case distribution according to gender was almost identical between groups, with 40 female and 39 male patients.

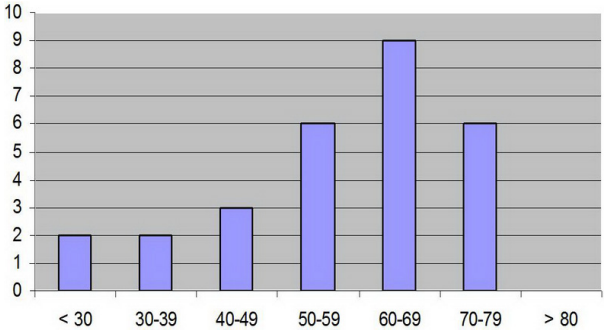

Figure 1 – ***Case distribution according to age group.***

Macroscopic features in GISTs

Several macroscopic features were followed in our study: maximum tumor size, tumor localization within different segments of the digestive tract or retroperitoneal, macroscopic aspect, secondary alterations on the cross-section surface or ulceration of the mucosal layer.

Regarding the maximum tumor size, in 39% of the cases, tumors were large, with dimensions between 5 and 10 cm, and in 32 cases, their size was medium, comprised between 2 and 5 cm. At the extremes, we found 11% of the tumors to be under 2 cm and, respectively, 18% had sizes over 10 cm.

From the localizations point of view, the most involved organ was the stomach (30 cases), followed by the small intestine (21 cases). The rarest localization of the primary tumor was the esophagus (two cases) and the large intestine (eight cases). Eighteen cases from the total of 79 comprised in our study were retroperitoneal, thus rendering this particular localization a rather rare occurrence. We followed the distribution of the small intestine primary tumors according to its segments. Half of these 21 cases were situated within the duodenum (10 cases), six in the jejunum and five in the ileum.

Macroscopically, 75% of the tumors were nodular (single or multiple nodules), 15% were exophytic, and few were polypoid (6%) or infiltrative (4%). Most tumors had a whitish color (81%), others were grayish (11%) or, less frequently, brown (5%). The cross-sectional surfaces of the tumors were assessed in order to identify macroscopic secondary alterations (tumor necrosis, mucosal ulceration, cystic degeneration, myxoid areas, hemorrhage, and calcifications). The most frequently encountered modification was tumor necrosis (33 cases), which significantly correlated with tumor size (p=0.0217). Mucosal ulceration was encountered in 24 of the 61 cases, and it also significantly correlated with tumor size (p=0.0358).

Microscopic features in GISTs

We assessed several microscopic features of the GISTs, as follows: tumor localization within the wall of the digestive tract, morphologic features, general secondary features in tumor development and metastases.

Microscopic localization within the wall of the digestive tract was assessed through careful examination of the histological sections pertaining to each case. Most of the tumors (34 cases) involved the whole thickness of the digestive tract segment they were located in. Smaller

tumors involved the submucosal layer (12 cases) or the muscularis propria (18 cases). GISTs located within the serosa were extremely rare. We encountered only one case of such tumor.

The study of the morphologic features revealed that most GISTs were spindle-cell tumors (67%) (Figure 2), followed by tumors with epithelioid arrangement (13%). 9% of the cases were mixed tumors (spindle cell and epithelioid) and myxoid forms, respectively, and in two cases the tumors had a signet ring cell aspect.

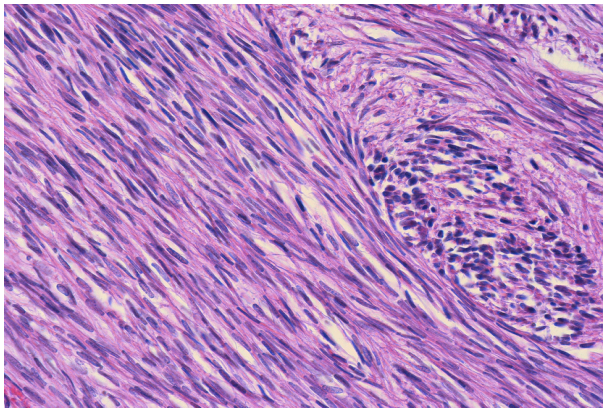

Figure 2 – ***GIST with spindle-cell features, ob. 10 ×.***

When analyzing the relationship between the tumors microscopic features and their localization, we noticed that the spindle-cell aspect prevails in all localizations, including the retroperitoneal one, while epithelioid and myxoid GISTs are more characteristic for the stomach. Signet ring cell GISTs appeared exclusively within the small intestine, while mixed aspects were slightly predominant at this location. Since most GISTs were either spindle-cell or epithelioid, we analyzed the distribution of these architectural features linked to the tumors' localization and have found no statistically significant difference between them.

We have encountered only one case of synchronous digestive tract tumors in our study, since these tumors are very rare. The GIST/GANT (gastrointestinal autonomic nerve tumors) variant, described as a tumor with particular microscopic features (aspects of neural differentiation), was present in 16% of the GISTs.

The general secondary features followed in our study were cyto-nuclear pleomorphism, the presence of giant multinucleated cells and inflammatory infiltrate, the presence of metastases and secondary tumors in the surrounding structures. 39% of the cases had cyto-nuclear pleomorphism, while we encountered giant multinucleated cells in only nine tumors. As in 54% of the tumors the inflammatory infiltrate was present, we assessed this secondary feature in relationship with tumor size and found a statistically significant correlation (p=0.0445) between these two elements. Metastases were present in seven cases, of which three were hepatic and four located in the lymph nodes. Local metastases were assessed by determining the location of the primary tumor in relation with microscopically identical nodules located elsewhere. Thus, we defined a local metastasis as the presence of epiploic nodules with a primary tumor located within the stomach, or a primary tumor located in the intestine with secondary tumors within the mesentery and vice versa. According to these criteria, we found six such cases, of which in five the primary tumor was located in the intestine and the secondary tumor nodules within the mesentery, and in one case the primary tumor was within the stomach and had secondary tumor nodules within the omentum.

Assesment of malignancy degree in GISTs

We studied the malignancy potential of the tumors based upon literature data. The two major criteria for warranting GISTs a certain degree of malignancy were the number of mitoses per 50 high power fields (HPF) and the maximum size of the tumor, given by the largest dimension of the tumor expressed in mm.

The number of mitoses was very carefully assessed, given its value as a major prognostic factor. An impressive 32% of the GISTs analyzed had a high mitotic activity (more than 10 atypical mitoses/50 HPF) at the time of diagnosis (Figure 3).

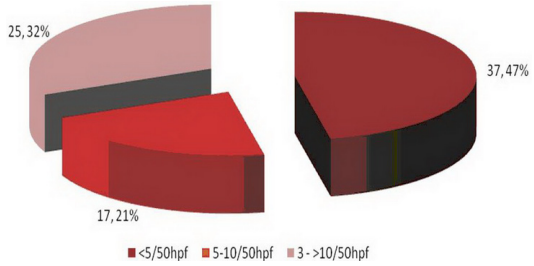

Figure 3 – ***GIST distribution according to the number of mitoses.***

Descriptive analysis showed that in the group of GISTs with <5 mitoses/50 HPF the average number of mitoses was approximately 2/50 HPF, in the group with 5–10 mitoses /50 HPF it was 7.52 mitoses/50 HPF, and in the group with >10 mitoses/50 HPF the average number of mitoses was 22.8/50 HPF.

The results regarding maximum tumor size as the second major prognostic factor were described above, within the subchapter concerning macroscopic features in GISTs (Table 2).

Table 2 – ***Descriptive analysis of tumor size in GISTs***

	Tumor size [mm]			
	Minimum	**Maximum**	**Mean value**	**No. of cases**
GIST <2 cm	6	15	11.22	9
GIST 2–5 cm	20	50	36.12	25
GIST 5–10 cm	51	100	76.45	31
GIST >10 cm	105	200	140.35	14

There was no statistically significant correlation between the number of mitoses and maximum tumor size (p=0.2462760 – p=0.623958).

Based upon these two major criteria, the tumors included in our study were classified as follows: seven cases (9%) were GISTs with very low degree of malignancy, 17 (21%) were GISTs with low degree of malignancy, and 18 (23%) were GISTs with intermediate degree of malignancy. The bulk of the cases (37/47%) were GISTs with high degree of malignancy. The correlation between the number of mitoses and the malignancy degree of the tumors revealed a statistically significant difference between

the number of mitoses in tumors with very low degree of malignancy and those with intermediate malignancy (p=0.026), respectively tumors with high degree of malignancy (p<0.05). Similarly, we found a statistically significant difference between the number of mitoses in tumors with a high degree of malignancy and those with intermediate degree (p=0.0002) and with a low malignancy (p<0.05), respectively. There was a statistically significant correlation between the degree of malignancy and tumor size in all cases (p<0.05).

We attempted to ascertain several secondary criteria that would be useful in classifying GISTs into different degrees of malignant potential by assessing correlations between these criteria and various morphologic features of the tumors. Regarding patients' age as a determining factor of malignancy in GISTs, we found that the number of intermediate and highly malignant tumors grows progressively towards the mean age of 60 years, reaching a peak in the 60–69-year-old group, after which it decreases. There was no statistically significant correlation between age and the degree of malignancy (p=0.4585). Patients' gender and malignancy degree showed no statistically significant correlation between them (p=0.2647). No statistically significant correlation appeared between the degree of malignancy and tumor localization (Figure 4), excepting retroperitoneal and small intestine GISTs (p=0.039).

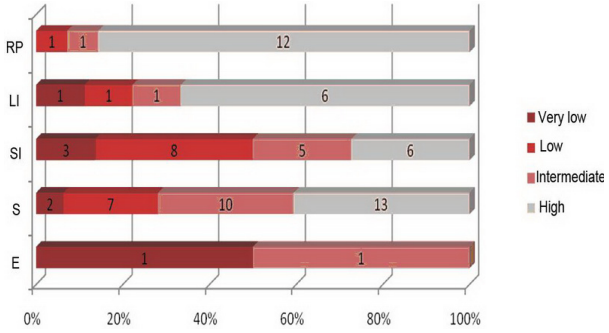

Figure 4 – ***Case distribution according to malignancy degree and localization.***

Tumor invasion of the mucosa was absent in very low malignancy GISTs, but showed a progressive increase in the other degrees of malignancy. Thus, from the total of 24 cases two were low malignancy GISTs, six were intermediate malignancy GISTs, and 16 were highly malignant GISTs. Comparative statistical analysis revealed a statistically significant difference between very low (p=0.0303) and low (p=0.0370) malignancy tumors *vs.* highly malignant tumors. Relative risk was very low (r=0.2667 and r=0.000, respectively). Although no significant value was revealed by statistical analysis in the case of intermediate and high malignancy GISTs, relative risk was high (r=0.7500).

The comparison between tumor necrosis and the degree of malignancy showed that the presence of the former increases steadily with the latter. Necrosis was absent in all very low malignancy GISTs but present in four low malignancy GISTs, eight intermediate malignancy GISTs and 21 high malignancy GISTs. Comparative statistical analysis revealed a statistically significant difference between very low (p=0.0386) and low (p=0.0094) malignancy and, respectively, high malignancy GISTs. Nevertheless, relative risk was low (r=0.3569 and r=0.000, respectively). The comparison between intermediate and high malignancy GISTs yielded no statistically significant difference, with a high relative risk (r=0.7172).

Assessment of GIST immunohistochemical features

In order to study the immunohistochemical features of the GISTs we used two categories of antibodies: some with high specificity for GISTs, such as CD117 and CD34, and others for differential diagnosis, namely SMA (specific for smooth muscle tumors) and S100 (specific for peripheral nerve sheath tumors), since these two types of tumors are most oftenly misdiagnosed as GISTs.

Seventy-seven of our 79 cases of GISTs were CD117 positive (Figure 5), with only two negative tumors. This yields a 97% rate of positivity, demonstrating a high specificity for this type of tumors (s=0.9746).

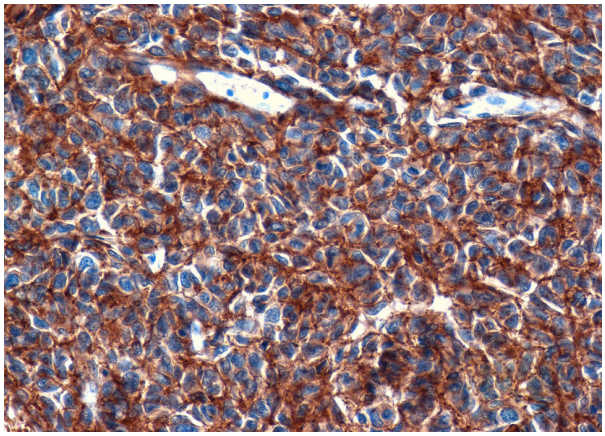

Figure 5 – ***GIST with epithelioid features, CD117 positive stain, ob. 20×.***

CD34 stain was positive in 50 cases (Figure 6) and negative in 29 cases, showing a 63% rate of positivity and thus a moderate specificity (s=0.6329). Only 19 of 79 cases showed positivity for SMA, with the remaining 60 cases being SMA-negative. The rate of positivity was, therefore, 24%, which translates into a low specificity (s=0.2405). 13% of the tumors were S100-positive (10 cases), while 87% were negative, yielding a very low specificity for GISTs (s=0.1265).

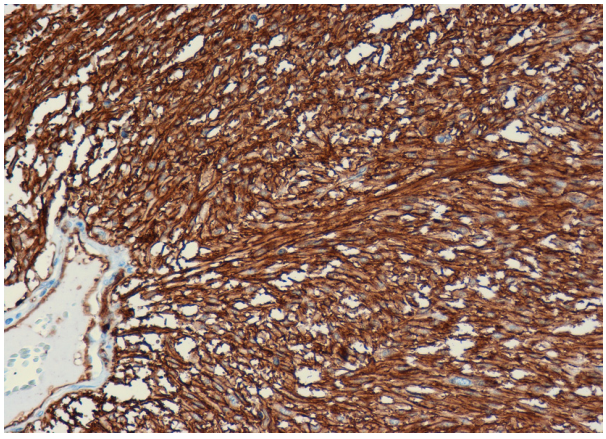

Figure 6 – ***GIST, CD34 positive stain, ob. 10×.***

Immunoexpression assessment of the four antibodies in relation to the macroscopic localization of the tumor (Table 3), did not revealed a statistically significant interrelation between the two evaluated parameters. Likewise, we have not found a statistically significant correlation in case of the malignity degree of GISTs and immunoexpression of the antibodies (Table 4) included in the study.

Table 3 – ***Immunoexpression assessment of the four antibodies in relation to the macroscopic localization of the tumor***

Localization	CD117		CD34		SMA		S100		Total
	-	+	-	+	-	+	-	+	
Esophagus	0	2 (2.6%)	1 (3.4%)	1 (2%)	1 (1.7%)	1 (5.3%)	2 (2.9%)	0	2
Stomach	1 (50%)	29 (37.7%)	9 (31%)	21 (42%)	25 (41.7%)	5 (26.3%)	28 (40.6%)	2 (20%)	30
Small intestine	0	21 (27.3%)	8 (27.6%)	13 (26%)	14 (23.3%)	7 (36.8%)	15 (21.7%)	6 (60%)	21
Large intestine	1 (50%)	7 (9.1%)	4 (13.8%)	4 (8%)	5 (8.3%)	3 (15.8%)	7 (10.1%)	1 (10%)	8
Extra gastrointestinal	0	18 (23.4%)	7 (24.1%)	11 (22%)	15 (25%)	3 (15.8%)	17 (24.6%)	1 (10%)	18
Total	2	77	29	50	60	19	69	10	79
p	0.425		0.850		0.411		0.280		

Table 4 – ***Correlation of the malignity degree of GISTs with immunoexpression of the antibodies included in the study***

Grade	CD117		CD34		SMA		S100		Total
	-	+	-	+	-	+	-	+	
1	0	7 (9.1%)	1 (3.4%)	6 (12%)	4 (6.7%)	3 (15.8%)	5 (7.2%)	2 (20%)	7
2	0	17 (22.1%)	6 (20.7%)	11 (22%)	14 (23.3%)	3 (15.8%)	16 (23.2%)	1 (10%)	17
3	1 (50%)	17 (22.1%)	5 (17.2%)	13 (26%)	15 (25%)	3 (15.8%)	16 (23.2%)	2 (20%)	18
4	1 (50%)	36 (46.8%)	17 (58.6%)	20 (40%)	27 (45%)	10 (52.6%)	32 (46.4%)	5 (50%)	37
Total	2	77	29	50	60	19	69	10	79
p	1		0.350		0.501		0.478		

Due to the high and, respectively, moderate specificity of CD117 and CD34 in the positive diagnosis of GISTs, we attempted to assess the expression of these antibodies in relationship with the tumors' microscopic features. Our results revealed a statistically significant difference between the two antibodies when taking into account the most frequent microscopic forms (Table 5), i.e., spindle cell, epithelioid and mixed tumors.

Table 5 – ***Statistical assessment of immunoexpression of CD117 vs. CD34 in most frequent microscopic forms***

CD117 *vs.* CD34	Sensitivity	*p*-value
Spindle-cell	0.5795	0.0005
Epitheloid	0.7143	0.0108
Mixed	0.7778	0.0210
Signet ring cells	0.6667	1.0000
Myxoid	0.5385	1.0000

Discussion

The last decade was a very controversial period for GISTs, in which immunohistochemical and molecular biology methods of study have established important diagnostic, prognostic and treatment criteria for these mesenchymal tumors [8]. The advent of new high specificity and sensitivity antibodies in current practice has allowed the establishment of GISTs immunohistochemical profile, which is a very important positive diagnosis criterion [9–13]. Genetic studies have described the most frequent mutations in GISTs, rendering them the cornerstone of tumor evolution assessment and therapy management according to specific mutations present in each GIST case [14–16].

We assessed within our study a series of specific and non-specific GIST features and compared our results with data in the literature.

After analyzing the data regarding general GIST features, we can conclude that these tumors appear predominantly after 50-year-old, with a maximum incidence around 60-year-old, and they do not have a predilection for any of the genders [16–19].

GISTs can appear in any segment of the digestive tract, involving the stomach, the small intestine, the esophagus and the large intestine in decreasing order of frequency [15, 20]. These tumors can also involve the retroperitoneum [21, 22]. Data in the literature shows that, as far as the small intestine is concerned, the most frequent localization is the jejunum, followed by the ileum and duodenum [23, 24]. In our study, however, this distribution was different. Thus, of the 20 GISTs located in the small intestine, half were situated in the duodenum, followed by those in the jejunum and ileum, with an insignificant difference between the latter.

From the macroscopic point of view, most of the tumors in our study were nodular (single or multiple), whitish tumors. The majority of cases had secondary non-specific alterations of the cross-section surface, with the most frequent being tumor necrosis [25, 26]. We established that this modification involves tumors over 5 cm in size. Cases with cystic and

myxoid degeneration were rare, and hemorrhage and calcifications were exceptional. In tumors located in the gastrointestinal tract, macroscopically visible mucosal ulceration also pertained to tumors larger than 5 cm.

Microscopic case assessment revealed that most tumors (34 cases) involved the whole thickness of the gastrointestinal wall [17, 26]. This finding can be explained by the fact that GISTs have a silent clinical evolution that allows tumors to attain rather large dimensions, as also revealed in our study, wherein most GISTs were larger than 5 cm. Smaller tumors tend to involve first the muscularis propria and than the submucosa. The most frequent cytomorphologic aspect was that of spindle-cell tumors, followed by epithelioid tumors. Other variants appeared less frequently or exceptionally (GANT) [26].

Assessment of the general secondary microscopic features revealed that cytonuclear pleomorphism and giant multinucleated cells were not common in GISTs [16, 17], but chronic inflammatory infiltrate appeared in over half of the cases in our study. Comparative analysis between the presence of inflammatory infiltrate and tumor size showed that this feature appears in tumors over 5 cm in size. Metastases were rare but, although they were statistically non-significant, their localization contradicted the data available in the literature. Thus, even though GISTs rarely metastasize, they are reported to do so mainly in the liver and exceptionally in lymph nodes [27, 28]. This difference is probably explained by the fact that our study was carried out within a period in which the diagnosis of GIST was a relatively novel and rather unaccepted concept in Romania and, as such, it was misdiagnosed as other pathologic entities. We tend to believe that, due to these circumstances, there might have been cases in which patients were not subjected to targeted paraclinical investigations and the presence of metastases was overlooked.

From the malignancy criteria standpoint, most cases were larger than 5 cm and had a high mitotic activity. Nevertheless, we have not been able to establish a statistically significant correlation between these two factors. These results point to the fact that a small tumor can have a high mitotic activity and thus it can be classified as highly malignant and, conversely, that a large tumor does not always show a high mitotic activity or a high degree of malignancy. Hence, these two criteria of malignancy cannot be used individually, and must always be assessed in conjunction to one another. Literature also reports cases of small tumors with high mitotic activity that recidivate and metastasize in the liver or *vice versa* [29, 30].

A small number of cases classified according to the two previous criteria in our study fell into the category of very low malignancy GISTs. In exchange, a large number of tumors were highly malignant. As previously noted, this distribution is explained by the late appearance of clinical symptoms, which are non-specific, hence a late presentation of the patients for investigation and treatment. Descriptive statistic analysis of the number of mitoses in relationship with the degree of malignancy revealed that in the group of high malignancy GISTs the minimum number of mitoses was 2/50 HPF. This is an indicative of the fact that tumors over 10 cm in size but with low mitotic activity can also be included in the high malignancy GIST category, on the grounds of dimension criteria. Descriptive analysis of tumor sizes in various malignancy degree groups drew our attention on the intermediate and high malignancy tumors, whose minimum sizes were lower than the value assigned for very low malignancy tumors. Thus, the size of the smallest intermediately malignant GIST was 15 mm, whereas the smallest highly malignant GIST size was 12 mm.

We tried to establish a series of correlations between the degree of malignancy and various other parameters in order to ascertain the value of several potential secondary prognostic factors.

Some authors considered as additional prognostic factors in correlation with malignity the young age, female gender, small or large intestine GISTs, necrosis and invasion of the mucosa may be considered as additional prognostic factors [30–32]. In our study, only the invasion of the mucosa and tumor necrosis correlated with the degree of malignancy. A comparative approach revealed a statistically significant difference between the degrees of malignancy and small intestine and retroperitoneal localization of the tumor, respectively. In GISTs located in the small intestine, the ratio between low and high malignancy GISTs was 1:1, whereas no retroperitoneal GIST was classified as a very low malignancy tumor, one case was a low malignancy GIST, one was an intermediate malignancy GIST and 12 were highly malignant. We can conclude that retroperitoneal GISTs are most frequently very aggressive tumors. This conclusion also applies to GISTs located in the stomach and in the large intestine.

In our study, the number of tumors infiltrating the mucosa increased in parallel with the degree of malignancy and there was a statistically significant difference in the appearance of this infiltration between low and, respectively, high malignancy GISTs. The relative risk was also low, which denotes that an infiltrating tumor is very unlikely to be classified as a low malignancy GIST. Within the same context, although no statistically significant difference appeared between intermediate and high malignancy tumors, the relative risk was high, meaning that it is more likely for a tumor that invades the mucosa to be classified as highly rather than intermediately malignant.

We obtained similar results after the comparative analysis of the degrees of malignancy and tumor necrosis. Some authors include necrosis as a factor denoting a highly malignant tumor when grading GISTs [28, 30, 33].

Analysis of the immunohistochemical features show that, due to its positivity in a large number of cases, CD117 is a highly specific marker in the positive diagnosis of these tumors, a fact that results also from the comparative study carried out between the four antibodies evaluated in the three categories of mesenchymal tumors included in our study [28, 34]. Since CD34 positivity was lower, this antibody can be used as an additional, less specific marker, which can be

nevertheless used when CD117 staining is focal, overall reduced or absent. The comparative study of these two antibodies when taking into account the microscopic features of the tumor also revealed a statistically significant difference between them. As far as SMA and S100 were concerned, they are less useful in the positive diagnosis of GISTs but are highly valuable in differentiating these tumors from the macro- and microscopically similar smooth muscle tumors and peripheral nerve sheath tumors [10, 23, 35].

Conclusions

Although GISTs are rare tumors, they represent an important tumor category of mesenchymal origin with gastrointestinal localization due to the importance of a correct histopathological diagnostic, with direct implications on the prognosis and subsequent treatment of patients with such a tumor. Following our study, we may conclude that GISTs develop most frequently in persons around 60-year-old and localize mainly in the stomach. From microscopic point of view, most frequently they take the appearance of a spindle cell tumor, with low cytonuclear pleomorphism, while large sized tumors show an abundant chronic inflammatory infiltrate. The most correct appreciation of the malignancy character can be performed by using the two major criteria of classification: maximum size of the tumor and the number of atypical mitoses, criteria to that, based on our study, minor classification criteria could be added like tumor invasion of the mucosa and presence of tumor necrosis. The final diagnosis of GISTs is based on the immunoexpression of CD117 and CD34. SMA and S100, specific markers for smooth muscle tumors and peripheral nerve sheath tumors, that may have a very similar microscopic appearance with GISTs, were expressed in a much smaller percentage, their usefulness being reflected in the differential diagnosis of these tumors.

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