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A histopathological and immunohistochemical approach of surgical emergencies of GIST. An interdisciplinary study

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Abstract

The tailored approach to gastrointestinal stromal tumors (GISTs) has led to better prognosis for these types of tumors. Also, finding out GIST's pathology has led to a better understanding of oncogenesis and cancer therapy in general. The rapid expansion of molecular and pathological knowledge of GISTs has given this disease a promising future. We analyze 30 cases of GISTs operated on in our clinic with confirmed diagnosis by immunohistochemistry. Most of the cases were acute cases that required urgent surgical therapy. An extended analysis of these cases is performed in order to underline their special features. We recorded 17 GISTs of the stomach, 12 GISTs of the small bowel and one esophageal GIST. Of the 30 cases, 15 cases required urgent surgery presenting with GI bleeding or shock following intraperitoneal rupture and bleeding or intestinal obstruction. Of the 15 cases that required urgent surgery 12 cases presented with serosal involvement. Twenty-four cases presented spindle cell histology, four cases were epithelioid and two cases presented mixed cellularity. Although acute presentation of GISTs is not the rule, 15 of 30 of our cases required immediate surgery and a high proportion of them (12/15) presented with serosal involvement. Serosal involvement may warrant the need for a macroscopic classification of GISTs and correlation to therapy. While overall mortality was not high in our series, morbidity is affected by acute presentation, though not specifically pertaining to the diagnosis of GIST. Acute presentations were more frequent, in our series, for small bowel GISTs, compared to gastric GISTs. Serosal involvement was more frequent in the group with acute presentation compared with non-acute GISTs and was present at the most cases of small bowel GISTs with acute onset. The Ki-67 index showed no difference between acute and non-acute onset of GISTs.

Keywords: gastrointestinal stromal tumor, acute presentation, serosal involvement.

Introduction

Gastrointestinal stromal tumors (GISTs) are rare tumors with an estimated incidence of 1.5/100 000 persons per year [1]. This number accounts for lesions that have a clinical expression, the number of microscopic lesions that can be detected on pathologic specimens being much higher. A German study on consecutive autopsies revealed small (<10 mm) GISTs in 22.5% of individuals over 50-year-old [2]. A SEER (*Surveillance, Epidemiology, End Results*) cancer registry in the US study by Rubin *et al.* from 1993 to 2002 showed that overall incidence, prevalence and 3-year survival were 3.2/million, 16.2/million, and 73%, respectively [3].

GISTs were previously difficult to define due to the lack of specific markers (the expression of the KIT protein). Therefore, the majority of GISTs were wrong diagnosed as smooth muscle tumors (*e.g.*, leiomyoma and leiomyosarcoma) or as tumors of the nerve sheath origin (*e.g.*, Schwannoma and malignant nerve sheath tumors). The advancement of immunohistochemistry, molecular technology and the identification of KIT oncogene mutation in more than 80% of GISTs have improved the diagnostic rate and accelerated our understanding of GISTs. Probably due to better histological diagnosis, we also noticed an increased incidence of GISTs in recent years.

Because constitutive activation of KIT and PDGFRA has been demonstrated in GIST development, the inhibition of these activated kinases by Imatinib and Sunitinib has been verified to be effective for the treatment of this neoplasia. The approval of Imatinib mesylate, an oral inhibitor of KIT and platelet-derived growth factor receptor, alpha polypeptide (PDGFRA), to treat metastatic GIST by the *USA FDA* in 2002 has markedly changed the outcomes and treatment options for GISTs. The five-year survival rate after complete surgical resection was 50% before the era of molecular targeted therapy. The outcome of GISTs improved significantly after the more widespread use of Imatinib. In a large Taiwanese study, the 5-year observed overall survival increased from 58.9% during 1998–2001 to 70.2% during 2005–2008 (p<0.0001) [4].

The main prognostic factors identified are the size of the tumor (>10 cm), tumor location, the involvement of

the serosa, mitotic index (>5 per 50 HPF), nuclear atypia, the persistence of tumor residuals within the surgical resection margins, tumor rupture, c-kit mutation that may interfere with molecular target therapy efficacy and Ki-67 [5, 6].

The most frequent GISTs related emergency seems to be gastrointestinal bleeding. Other noted emergencies consist of intestinal obstruction, intraperitoneal hemorrhage, rupture and peritonitis [7].

The aim of our study, conducted in an Emergency Surgical Department, was to identify specific features of acute presentation of GISTs. We encountered grossly half of these tumors in an acute condition that required emergency surgery in their first 24 hours from admission.

Materials and Methods

Histopathological investigation

Case selection for the study batch

We have retrieved from our database, in queue, in an interval between January 1, 2008–December 31, 2012, 30 cases with archived formalin-fixed paraffin-embedded samples of GISTs, selected from patients with gut tumors.

The study batch consisted of 19 male and 11 female patients (gender ratio M:F = 1.72/1), with age ranging between 42 and 72 years (mean age: 62 years, SE ±3), 23 patients being city inhabitants and seven coming from rural environment.

All patients were admitted in the Department of Surgery, "St. Pantelimon" Emergency Clinical Hospital, Bucharest, Romania, between 2008 and 2012. Surgical procedures and biopsy analysis with histopathology investigation were performed at the same institution. Immunohistochemistry was done at the Department of Pathology, "Mina Minovici" National Institute of Legal Medicine, Bucharest, Romania.

The study has received ethical approval from the local ethics committee and written informed consent was signed before enrollment. Subsequently, tissue samples for microscopy analysis were taken after the informed consent, using a protocol approved by the local Bioethics Committee, in accordance to generally accepted international practice.

Tissue sampling and stains

Tissue specimens from the gut were taken for histopathology investigation. The fragments were harvested from esophagus, stomach (vertical and horizontal portion) and small bowel (jejunum and ileum). The selected tissue samples were fixed in 10% neutral buffered formalin (pH 7) for 24–48 hours and paraffin embedded. Sections were cut at 5 μm and stained with standard Hematoxylin–Eosin (HE) and van Gieson.

Immunohistochemistry

Immunohistochemical (IHC) analysis was done using sections displayed on slides treated first with poly-L-Lysine. IHC was performed on 3 μm thick sections from formalin-fixed paraffin-embedded specimens.

The method used was an indirect tristadial Avidin–Biotin complex technique, with a NovoLink Polymer detection system, which utilizes a novel control polymerization technology to prepare polymeric HRP-linker antibody conjugates, according to the manufacturer's specifications (Novocastra, UK).

Briefly, the procedure comprised: deparaffination in toluene and rehydration in alcohol series, washing in phosphate buffer saline (PBS), blocking with normal serum, for 5 minutes, incubation with primary antibody 60 minutes, incubation with post-primary block 30 minutes, then with NovoLink Polymer 30 minutes. Sections were further incubated with the substrate/chromogen 3,3'-diaminobenzidine (DAB) and counterstained with Mayers' Hematoxylin.

The antibodies used for IHC were: CD117, CD34, vimentin, α-SMA, S-100, Ki-67 (for details, see Table 1).

Table 1 – ***Antibodies used in IHC assessment***

Antibody	Clone	Dilution	Producer	Specificity
CD117	T 595	RTU	Novocastra	Cajal cells, mast cells
CD34	QBEnd/10	RTU	Novocastra	Cajal cells, vessels
Vimentin	V9	RTU	Novocastra	Stromal cells
S-100	Poly	RTU	Novocastra	Neural cells
α-SMA	α-sm-1	RTU	Novocastra	Smooth muscle actin
Ki-67	MM1	RTU	Novocastra	Proliferating index

RTU – Ready to use.

Antigen retrieval techniques (thermal or enzymatic pre-treatment) for some of the aforementioned antibodies were done, according to the producer's specifications. Both positive and negative controls were used.

Negative control was made by using a primary irrelevant antibody or by replacing the secondary antibody with phosphate-buffered saline (PBS). Positive control was made comparatively with the expression of antibody investigated in the peritumoral normal tissue structures (positive internal control on slides).

To ensure the reliability of the experimental study, internal quality control of histopathological and IHC techniques were performed as a part of an implemented and certified quality assurance system (SR EN ISO 9001/2008).

All slides were examined and photographed on a Zeiss Axio Imager microscope (Göttingen, Germany). Digital images acquired with Zeiss Axio Vision program have been processed and analyzed with ACDSee Pro Photo Manager (Washington DC), running under Windows Vista.

IHC assessment and statistics

The distribution of markers-positivity has been assessed using the modified Quick score method [8], which takes into account the intensity and distribution of the IHC reaction: negative (no staining) – 0; weak (only visible at high magnification) – 1; moderate (readily visible at low magnification) – 2; strong (strikingly positive at low magnification) – 3.

Descriptive statistics was used for uniform distributed data of the study batch for mean, median and standard error. Statistical analysis was performed in SPSS 13 software, running under Windows Vista. A value of $p<0.05$ was considered statistically significant.

Clinical and imagistic investigation

Patient charts, operative recordings, histological and immunohistochemistry results were used to gather data

for this study. The patients were treated by different teams and specialists from our Department so the treatment was not completely standardized. Following the admission in our Department, the patients were direct at discharge towards the territorial oncological specialist. We paid special attention to cases that presented with an acute clinical and biologic picture and required urgent surgical therapy. A correlation between several histological factors and the urgent nature of treatment has been attempted.

Location of tumors

Gastrointestinal stromal tumors can appear everywhere from the esophagus to the rectum, but most commonly they occur in the stomach and small intestine. Generally, 60–70% occur in the stomach, 25–35% in the small intestine, 5% in the colon, rectum or appendix, and 2–3% in the esophagus. Gastrointestinal stromal tumors are typically seen in adults, especially over 40 years of age. We encountered 17 tumors in the stomach, 12 of which in the vertical portion and five in the horizontal portion. Twelve tumors of the small intestine were identified, seven in the jejunum and five in the ileum. Only one case of esophageal GIST was found, the tumor being located in the upper third of the esophagus. Figure 1 shows the location of GIST tumors found in our study.

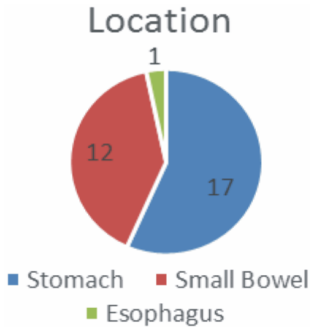

Figure 1 – ***Location of GIST tumors in our study.***

The clinical presentations of GIST are highly variable according to their location and size. The most frequent symptoms were anemia, weight loss, gastrointestinal bleeding, abdominal pain and mass-related symptoms. Patients with acute presentation of GISTs encountered acute abdomen, obstruction, perforation or rupture, peritonitis or important bleeding that required surgical intervention. We categorized patients with acute onset of GISTs, those who needed a surgical procedure (open or laparoscopic) within the first 24 hours from admission. Acute presentation and emergent surgery were recorded more frequently in the cases with small bowel tumors (nine of 12 cases).

Diagnostic

The diagnostic evaluation of GISTs is based on imaging techniques, with a special role of endoscopic examination because it is usually accessible when tumors are in the stomach, esophagus and large intestine. In addition, endoscopic ultrasonography also plays an important role in the diagnostic work-up of GISTs and is accurate and efficient. In general, externally bilging tumors are more common than intraluminal masses [9]. The diagnosis of small bowel GISTs deserves special attention due to the difficulties encountered in order to investigate the segment. Small bowel barium study is the most commonly used technique for detection of small bowel lesions, but diagnostic accuracy is 30–40% [10]. Endoscopic capsule (EC) was developed and routinely used in clinical practice since the beginning of 2000. It has since revealed its superiority for small bowel pathology. While EC is noninvasive and well tolerated, it is not capable of taking biopsies and performing therapeutic procedures. Akyüz *et al.* [11] report three cases of GISTs of the small bowel not detected by EC investigation but diagnosed by double-balloon enteroscopy. The authors conclude that double-balloon enteroscopy should be performed if there is a high clinical suspicion for small bowel pathology even if the capsule endoscopy is negative. Currently it is accepted that endoscopic biopsy is not necessary for diagnosis because surgical resection should be performed.

Preoperative diagnostic was established in elective cases by upper endoscopy, ultrasound, computer tomography or MRI. On the other hand, the patients with acute presentation were diagnosed intraoperative with gastric/small bowel mass.

According to the new TNM classification of GISTs [12, 13], we encountered the following stages for gastric GISTs: two cases were staged IA, three cases IB, four cases stage II, two IMA, three cases NIB, and three stage IV – lymph node involvement and two cases with metastasis (according to the new UICC classification). Regarding the small bowel GISTs, we found two cases of stage I, four GISTs stage II, one IMA, four NIB and two cases stage IV (lymph node involvement and one case with metastases).

Clinical aspects

Clinical presentation of gastric tumors (Table 2) was acute in six cases that presented with acute upper gastrointestinal (GI) bleeding with melena and hematemesis and required urgent surgery (within the first 24 hours).

Table 2 – ***Clinical findings of gastric GISTs***

Clinical findings	No. of cases
Abdominal pain	8
Dyspepsia	10
Weight loss	6
Fever	3
Acute upper GI bleeding	6
Anemia, chronic bleeding	3

Abdominal pain was recorded in eight cases, dyspepsia in 10 cases, weight loss was recorded for six patients and three patients presented with fever that did not respond to therapy and had no other etiology. All patients had endoscopy associated with biopsy except three cases from the six that required urgent surgery. Barium swallows were performed for three cases prior to endoscopy. Computed Tomography (CT) of the abdomen was performed in eight cases for staging of the extent of the disease and eventual distal metastases. Metastases to the liver were found in two cases that had significant weight loss and large tumors. One of the tumors invaded the pancreas and the hilum of the spleen (Figures 2 and 3). Of the six acute cases, five tumors were located in the horizontal portion of the stomach and one tumor in the vertical portion. Nine patients reported epigastric pain for several years before presentation.

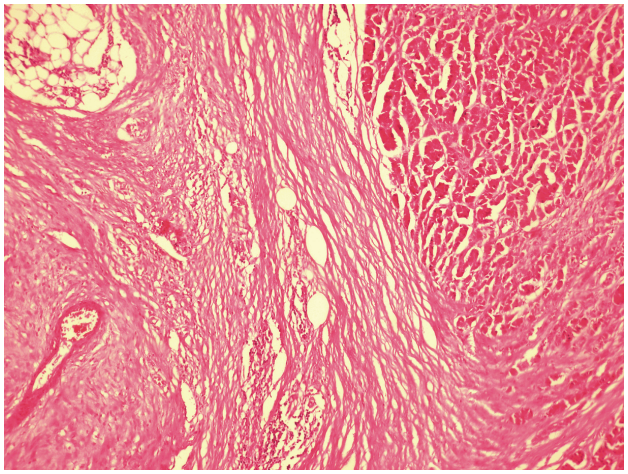

Figure 2 – ***GIST with spindle type cells with pancreatic invasion. HE staining, ×100.***

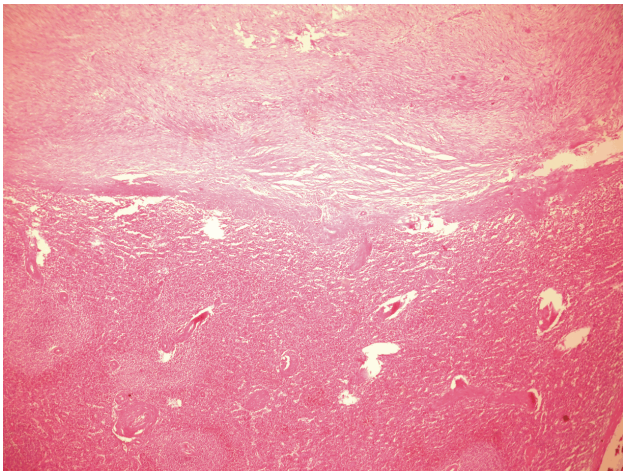

Figure 3 – ***GIST with spindle type cells with capsular spleen invasion. HE staining, ×40.***

Clinical presentation of small bowel GISTs is shown in Table 3.

Table 3 – ***Clinical findings for small bowel GISTs***

Clinical findings	No. of cases
Abdominal pain	11
Intestinal obstruction	7
Weight loss	8
Shock, intraperitoneal bleeding	2
Upper GI bleeding	1
Chronic anemia	2

Seven patients presented with intestinal obstruction (distended and painful abdomen, emesis, Rx presence of air-fluid levels) and two with signs of shock and evidence (ultrasound, diagnostic peritoneal lavage) of intraperitoneal bleeding. These nine patients required urgent surgery and were operated within the first 24 hours after admission. Two patients presented with chronic anemia not diagnosed by hematological tests, upper and lower GI endoscopy. One was diagnosed by CT and one by diagnostic laparoscopy. One patient presented with upper GI bleeding (melena) and was diagnosed by CT. Overall, 11 patients presented with abdominal pain and eight with weight loss. Three patients presented liver metastases and two patients presented epiploic tumors smaller than the primary site tumor.

Tumors were located throughout the small bowel with no correlation between type of presentation and location. Seven tumors were found in the jejunum and five in the ileum. Mean tumor size was 9 cm, the larger measuring 19 cm.

Surgical procedures (briefly)

Complete surgical resection with microscopically negative margins represents the standard of care for patients presenting primary resectable GISTs. Particularly, neo-adjuvant therapy for those with resectable disease is actually not recommended, although preoperative drug administration may be considered for patients with marginally resectable tumors and for those having potential resectable disease but at increased risk of significant morbidity. When small esophageal, gastric or duodenal nodules less than 2 cm in size are detected, endoscopic biopsy may be difficult; in these cases, laparoscopic or laparotomic excision may be elected in order to achieve a histological diagnosis. According to new guidelines, GISTs smaller than 2 cm must be regarded as essentially benign. For this reason, the standard approach to these patients relies on endoscopic ultrasound assessment and then follow-up. For lesions larger than 2 cm the standard approach is biopsy/excision.

We paid special attention to cases that presented with an acute clinical and biologic picture and required urgent surgical therapy. A correlation between several histological factors and the urgent nature of treatment has been attempted.

All 12 tumors from the vertical portion and one from the horizontal portion were treated by total gastrectomy. One of these cases associated distal pancreatectomy and splenectomy for a tumor invading the tail of the pancreas and the hilum of the spleen. Three of the five tumors from the horizontal portion were treated with distal gastrectomy and one lying on the greater curvature with a wedge gastric resection (CT showed no distal metastases, tumor size of about 3 cm with no bleeding). Mean size of the tumors was 7 cm with the greater being measured at 22 cm on the greater curvature. The six cases with acute bleeding had a mean size of 5 cm, the larger measuring 7 cm.

The standard surgical treatment for small bowel tumors was segmentary enterectomy in 11 cases, followed by mechanical anastomosis. One case, with terminal ileum tumor required right hemicolectomy.

We achieved negative surgical margins in all small bowel resections – R0 resections. Only one gastrectomy for gastric GIST had positive microscopic surgical margins (R1 resection).

The two cases with hemoperitoneum were diagnosed with intraperitoneal ruptured GISTs of the small bowel. Intestinal obstruction was produced in five cases by extralumenal manifestations (adhesions, volvulus, and extrinsic compression) and in only two cases by intraluminal development of the tumor (Figure 4).

The procedure performed for the esophageal tumor was esophageal resection and esophageal reconstruction

with stomach. The tumor was 2 cm in size, had no CT evidence of distant disease or nodal involvement.

The specimens for histological analyses were all surgically obtained by total excision of the masses. The tissue was placed in fixative shortly (<30 minutes) after surgical removal, and over-fixation (>24–48 hours) was avoided.

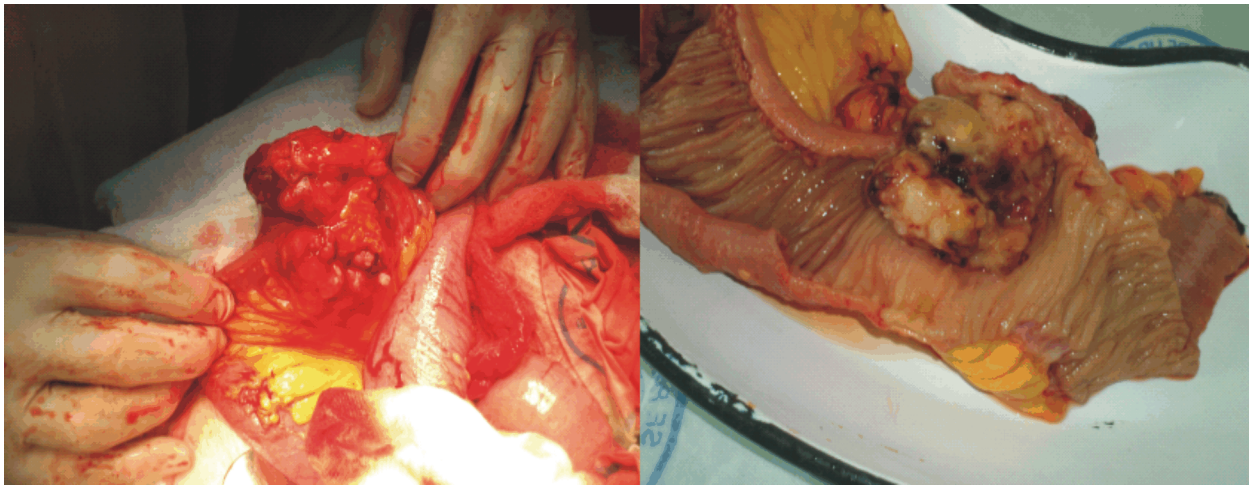

Figure 4 – ***Small bowel GIST, intraoperative finding and resection specimen; intraluminal growth and serosal involvement.***

Clinical surveillance (follow-up)

Short-term follow-up revealed no major complications in 28 cases with good recovery. We recorded two deaths; one in a patient with extensive disease and liver metastases that presented with chronic anemia with a small bowel tumor, and one with a ruptured, hemorrhagic tumor of the small bowel. However, acute presentation is not the rule and long-term follow-up is more important for determining the impact of different factors like serosal involvement and intraluminal growth on survival and response to Imatinib.

The nature of our department, that of emergent surgery, did not allow for long-term follow-up and as such the matter will not be discussed in this paper. All the cases were referred to the oncology department.

Acute presentation of GISTs

As mentioned before, we defined acute presentations as those cases that required an emergency surgical procedure within 24 hours from admission.

Among the 12 cases of small bowel GISTs, there were nine cases of acute presentation. A lower proportion of acute onset was observed at gastric GISTs (only six of a total of 17 cases).

Results

Histopathological investigation

Gastric GISTs were recorded in 17 cases: 14 cases had spindle cells showing foci of short-whorls or fascicles arrangement (Figure 5) and three cases had epithelioid cells.

Intestinal GISTs were recorded in 12 cases, seven in the jejunum and five in the ileum, with a mean tumor size of 8 cm, the larger measuring 19 cm. Nine cases of GIST (75%) have shown spindle-cells, two cases had a mixed type pattern and one was epithelioid (Figure 6).

In gastric GISTs, all cases had c-KIT/CD117 positivity at immunohistochemistry and eight were CD34 positive. Five cases that presented with acute bleeding were spindle type GISTs and one was epithelioid.

CD117 stained positive, diffusely or focally, in tumor cells showing cytoplasmic or perinuclear dot reaction. The IHC reaction was noticed in all cases, with various intensities, both in spindle cell and epithelioid type of tumors (Figures 7 and 8). Mast cells were used as positive intern control reaction.

CD34 was positive in 47% of cases, with moderate or strong cytoplasmic reaction in tumor cells (Figure 9). Capillary vessels were used as positive intern control.

In some cases, tumor cells showed smooth muscle differentiation, staining positive for α-SMA (Figure 10) or neural differentiation, staining positive for S-100 (Figure 11).

IHC for vimentin was mild or moderate in the cytoplasm of tumor cells (Figure 12).

In intestinal GISTs, all tumors were c-KIT/CD117 and CD34 positive, with moderate or strong IHC reaction in the cytoplasm of tumor cells. DOG1 was investigated in nine cases of small bowel GISTs and was found positive in all cases, including all seven cases of intestinal obstruction.

The case with esophageal GIST presented to our department after a one-year history of dysphagia and was diagnosed by upper GI endoscopy. The procedure performed was esophageal resection and esophageal reconstruction with stomach. The tumor was 2 cm in size and had no CT evidence of distant disease or nodal involvement. Microscopic, the tumor showed spindle cells and was c-KIT positive.

Overall, Ki-67 had a variable IHC reaction in the tumor cell nuclei, ranging from 5% to 25%.

Clinical and imagistic investigation

Acute presentation was much more frequent among small bowel GISTs, compared to gastric GISTs ($p<0.05$). The main characteristics of GISTs with acute presentation are shown in Table 4.

One of our patients, a 68-year-old female, presented as an ileo-ileal intussusception (Figure 13), which is not a unique case in the literature [14]. There was no correlation between type of presentation and location on the small bowel (jejun *vs.* ileon).

We noticed that serosal involvement was present in seven of nine cases of small bowel GISTs with acute presentation, respectively two of six cases for the gastric location, with a statistically significant difference between these two groups. Furthermore, serosal involvement was more frequent in GISTs with acute presentation (nine from 15 cases), compared to the non-acute group (three from 15 cases). This difference has also statistically significance.

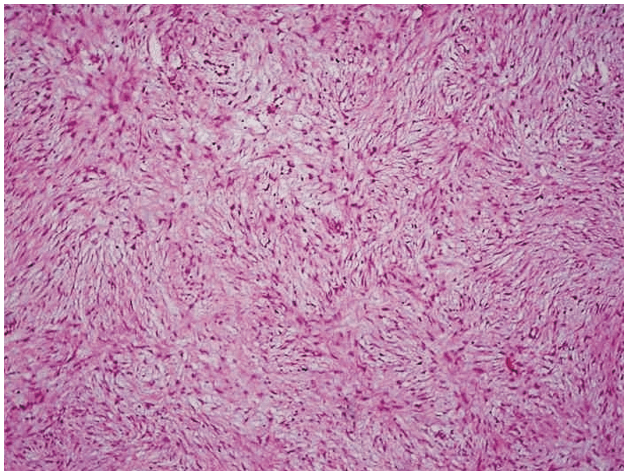

Figure 5 – ***Gastric GIST with spindle type cells. HE staining, ×200.***

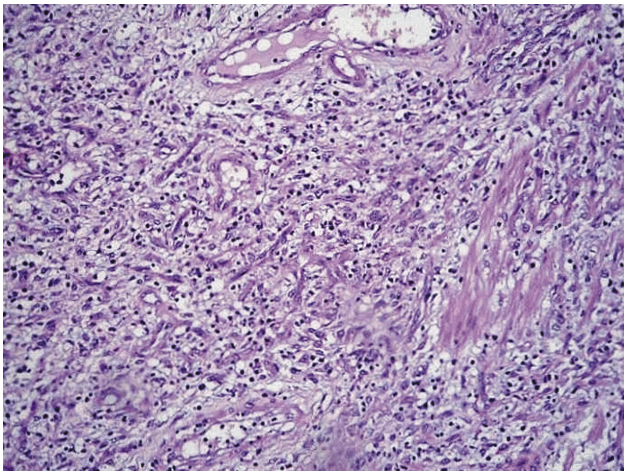

Figure 6 – ***Small bowel GIST with epithelioid-type cells. HE staining, ×200.***

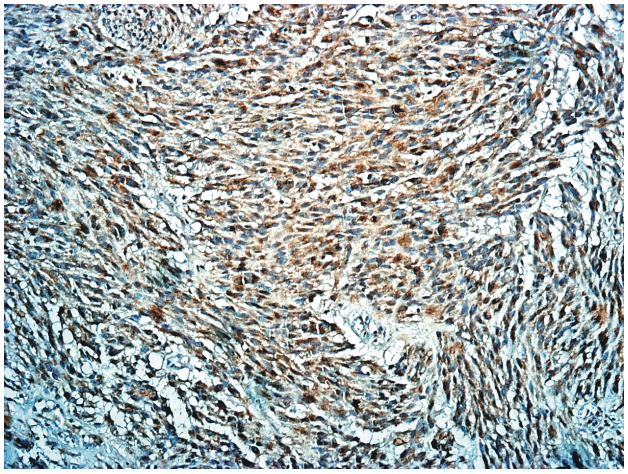

Figure 7 – ***GIST with spindle cells staining positive for CD117. IHC, ×100.***

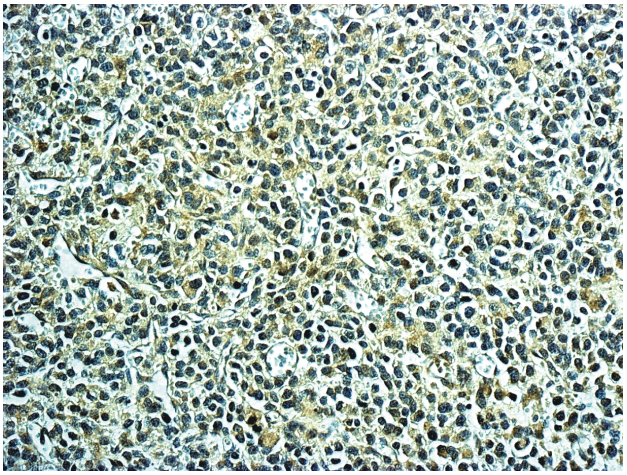

Figure 8 – ***GIST with epithelioid cells staining positive for CD117. IHC, ×200.***

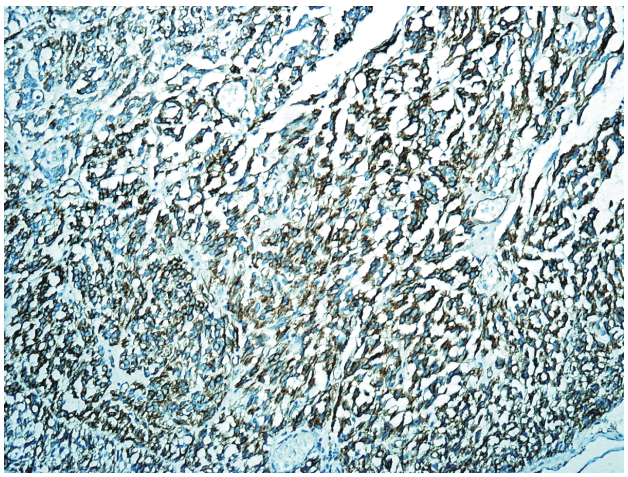

Figure 9 – ***GIST with tumor cells staining positive for CD34. IHC, ×100.***

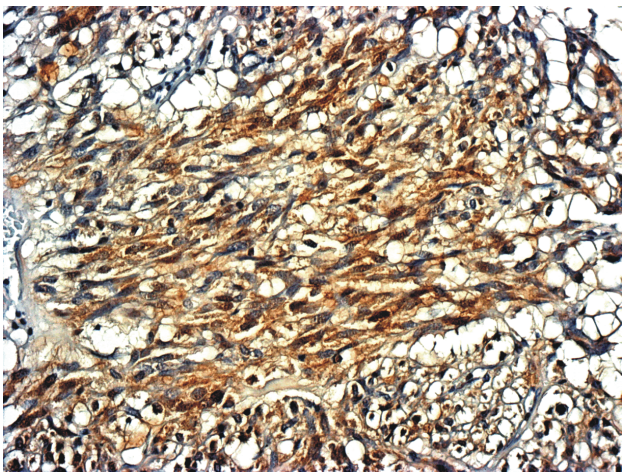

Figure 10 – ***GIST with muscular differentiation, tumor cells staining positive for α-SMA, ×200.***

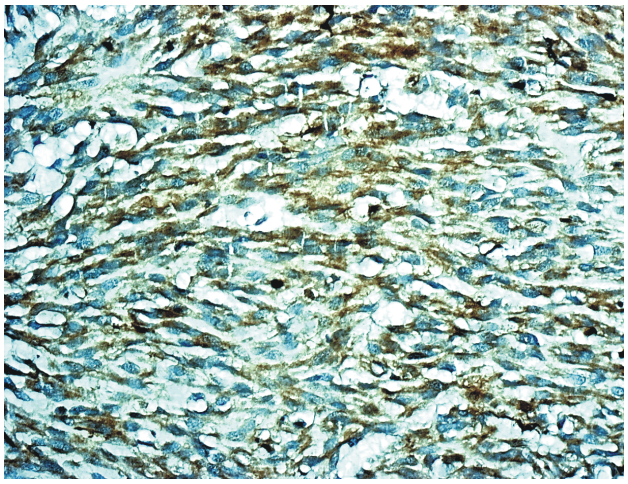

Figure 11 – ***GIST with neural differentiation, tumor cells staining positive for S-100. IHC, ×200.***

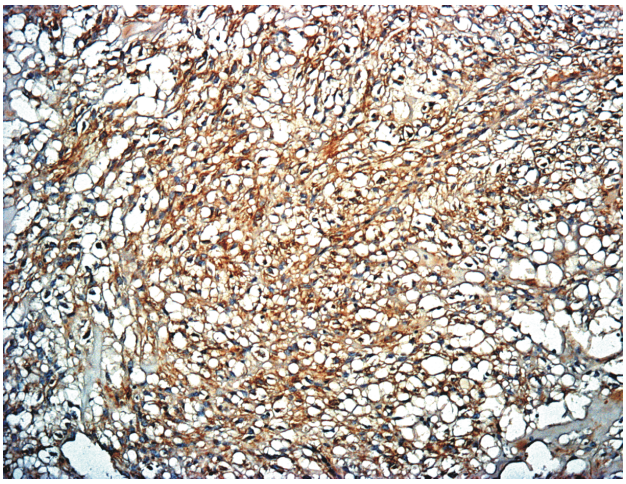

Figure 12 – ***Scattered tumor cells of GIST staining focally positive for vimentin. IHC, ×100.***

Table 4 – ***Characteristics of GISTs that required urgent surgical therapy***

Acute presentation	No. of cases	Location	Mean size [cm]	Metastatic disease	Serosal involvement	Light microscopy	KIT+
Small bowel	9	–	6	2	7	Mostly spindle cell type	All
Gastric	6	5 horizontal 1 vertical	5	1	2	Mostly spindle cell type	All

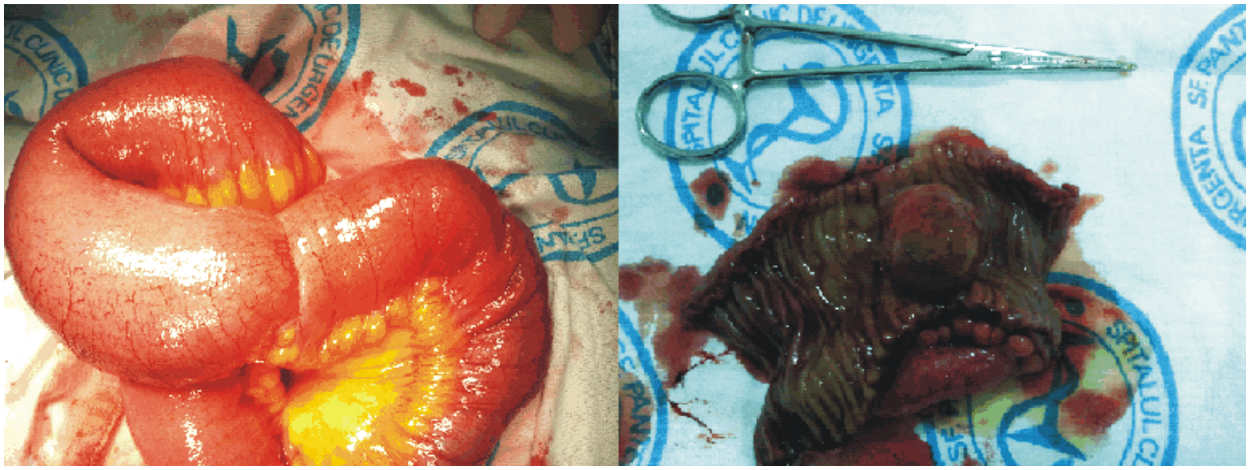

Figure 13 – ***Ileoileal intussusception caused by a small bowel GIST.***

Discussion

Immunohistochemical diagnosis is based mainly on CD117 (immunoreactivity for KIT) and several other markers: DOG1, CD34, h-caldesmon, S-100, desmin, and cytokeratins 8 and 18. The differential diagnosis should be made with leiomyoma, leiomyosarcoma, schwannoma, fibromatosis, inflammatory myofibroblastic tumor, inflammatory fibroid polyp, carcinoma and melanoma (for this latter condition HMB-45, Melan-A, or S-100, easily helps to resolve this differential) [15]. In differentiating from smooth muscle tumors smooth muscle actin and desmin are salutary [16]. Some patients may develop GIST as well as other types of cancer [17]. We did not meet such cases in our series.

Acute presentations of GISTs were more frequent in the intestinal group compared to the gastric location (p=0.017, Student's t-test). For statistical interpretation, regarding the relatively low number of patients in our series, we used Student's t-test and a value of p<0.05 was considered statistically significant. In a larger series of the literature (92 patients), Sorour *et al.* [7] reported more than 50% of emergencies for the gastric location of GISTs. We had a high proportion of small bowel obstruction (seven of nine cases with acute onset of small bowel GISTs), different from most studies reported, which stated on the first place gastrointestinal bleeding. Morrison and Hodgdon explained that for GIST tumors GI bleeding is the more common acute presentation, with bowel obstruction being less common. The majority (65%) of GIST tumors are seen in the stomach, which probably accounts for this phenomenon as the stomach is a highly vascular organ not easily obstructed. Obstruction can be the result of several different characteristics of these tumors: (1) continued growth of the lesion with direct occlusion of the bowel; (2) intussusception with the tumor acting as the lead point results in obstruction; or (3) a volvulus-like torsion of the bowel around the tumor, if its growth pattern is extraluminal [18].

Serosal involvement was more frequent in the group of acute presentation GISTs (nine of 15), compared to non-acute presentation group (three of 15) (p=0.012, Student's t-test). Serosal involvement was more frequent in our series at the patients with acute presentation of small bowel GISTs (seven of nine cases) compared to those with acute presentation of gastric GISTs (two of six cases). The difference is statistically significant (p=0.048, Student's t-test). Data are concordant with those of the literature, serosal involvement being well known as a negative prognostic factor. As also shown by Agaimy *et al.* [19] serosal involvement may have a negative impact on the prognosis, recurrence and survival of GIST patients.

The mean size of the gastric GISTs in our study was 7 cm, with the greater being measured at 22 cm on the greater curvature. The six cases with acute gastric bleeding had a mean size of 5 cm, the larger measuring 7 cm. Mean small bowel tumor size was 9 cm, the larger measuring 19 cm. The nine cases with acute presentation had a mean size of 6 cm. There were noticed no statistically significant differences of tumors' size. Reported tumor size in the stomach varies from a few millimeters to more than 40 cm with a mean size of 6 cm in the largest reported series [20]. Apparently, the tumor size is one of the factors contributing to clinical symptoms. A population-based study showed that the tumor size is 8.9 cm in patients with clinical symptoms, which is about 70% of GISTs studied, 2.7 cm in patients without clinical symptoms, 20% and 3.4 cm in patients with GISTs detected at autopsy, 10% [1]. Another study on small bowel GISTs reported the largest tumor diameter varying from 3 to 30 cm (median: 8.8 cm) [21].

Aggressive GISTs have a defined pattern of metastasis to the liver and throughout the abdomen or both. Lymph node metastasis is rare. Spreading to the lung and bone in advanced cases has been reported [22–24]. Metastasis often occurs 10–15 years after initial surgery. In our series, metastases to the liver were found in three cases that had significant weight loss and large tumors, two of them located on the stomach and one on the small bowel. We found only three cases (from 30, corresponding to 10%) with lymph node involvement (two for gastric tumors, and one for a small bowel tumor), which proved once more to be a rare condition, as reported in literature [25]. There are also studies that report a higher rate, close to 20% [26].

Acute presentation of GISTs poses problems in therapeutic tailoring, recovery and starting specific therapy. Our study showed that small bowel tumors are likely to present more often in an acute setting and require urgent surgical therapy. Acute presentation for gastric locations was upper GI bleeding although high GI tract obstructions are reported and possible [27]. For the small bowel, intestinal obstruction was by far the most frequent indication for urgent surgery. The mechanisms for obstruction rarely are those resulting from intraluminal growth. Adhesions, volvulus, extrinsic compressions are more frequent. Among intestinal GISTs obstruction was produced in five cases by extraluminal manifestations (adhesions, volvulus, and extrinsic compression) and in only two cases by intraluminal development of the tumor. Tumor rupture with intraperitoneal bleeding was also a major finding that required immediate specific therapy and was found in two cases of small bowel tumor although gastric locations can lead to this as well.

Esophageal GISTs are rare, they usually exhibit a male predominance, more often present with dysphagia, typically arise in the distal esophagus (middle or lower third), often involving the esogastric junction, usually small sized [28]. We encountered only one case, a male patient, with a small esophageal GIST (2 cm) located on the distal esophagus. We did not encountered duodenal cases, although some authors report half of small bowel GISTs with this location [29].

The mitotic index Ki-67 is well known as a poor prognostic factor, a value above 10% has been cited by most studies as indicating a poor outcome and affecting long-term survival [30]. In our study, Ki-67 had an overall variable IHC reaction in the tumor cell nuclei, ranging from 5% to 25%. Its value showed no statistically significant difference between the group with acute presentation of GISTs and the non-acute one (p>0.05).

Conclusions

Although acute presentation is not the rule, half of our 30 cases required urgent surgical therapy within the first 24 hours from admission, probably due to the nature of our service. The instance of acute presentation can limit diagnostic studies and correct staging of the disease and can hinder surgical and medical therapy. The proportion of cases with acute presentation among the intestinal location of GISTs is statistically significant higher than the similar proportion among gastric GISTs. The principal mechanism of acute presentation of small bowel GISTs was extraluminal obstruction (five cases), rather than intraluminal growth of the tumor (two cases) or intraperitoneal rupture and hemoperitoneum (two cases). Gastric bleeding was the complication of all six gastric GISTs that required urgent surgery. Serosal involvement was more frequent, in our series, for the patients with acute presentation of GISTs, compared to the non-acute group, and for the patient with acute presentation of small bowel GISTs, compared to those with acute presentation of gastric GISTs, serosal involvement being well known as a negative prognostic factor. In our study, Ki-67 had an overall variable IHC reaction in the tumor cell nuclei, ranging from 5% to 25%. Its value showed no statistically significant difference between the group with acute presentation of GISTs and the non-acute one.

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