CASE REPORT

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# Giant gastrointestinal stromal tumor of the stomach

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**Abstract**

Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal malignancies of the digestive tract. Gastric localization is the most frequent. The aim of this study is to evaluate the importance of immunohistochemical factors (CD117, CD34, α-SMA, vimentin, p53, Ki67) in diagnostic and size tumor and mitotic activity as prognostic factors for these tumors. We present the case of a 66-year-old male patient with a giant gastric GIST. Like in the vast majority, the symptomatology in this patient has long been faint, despite the large tumor size, and when it became manifest, it was nonspecific. Imagery wise, the computer tomography (CT) scan was the most efficient, showing the origin of the tumor from the greater curvature of the stomach, its dimensions, as well as the relations with the other abdominal viscera. Surgery in this patient was en-bloc, according to the principles of GIST. The histological aspect is characterized by a proliferation of spindle cells positive for CD117 and CD34. Despite complete microscopic resection, the size of the tumor (25×20×27 cm) and the mitotic activity (21/5 mm$^2$) remains important relapse factor.

***Keywords***: gastrointestinal stromal tumor, proto-oncogene proteins c-kit, recurrence.

## Introduction

Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal tumors of the gastrointestinal tract. En-bloc surgery of the tumor is the primary treatment for GIST, which are resectable. Relapse is common and is caused by two main factors, namely the size of the tumor and mitotic activity [1]. GIST pathogenesis originates in the interstitial cell described by Cajal, the intestinal pacemaker cell which generates slow electrical waves and interposes itself between the intramural neurons and the soft muscle cells of the digestive tract [2].

Kit is a protoncogene, which encodes the transmembrane receptor CD117 [3]. Overexpression of Kit in the tumor cells results from constitutive activation of the Kit tyrosine receptor. Kit activation leads to intracellular signaling that causes increased cellular proliferation and cell survival leading to tumor formation [4].

Histologically, 95% of GISTs express the CD177 transmembrane receptor, which is the main immunohistochemical marker [5]. In GIST, which lacks the Kit mutation, 35% of them have a mutation on PDGFRA [6].

GIST can occur at any age but are more frequent around the age of 66–69 years. Many of GISTs remain undiagnosed due to lack of symptomatology or small size. In an investigation by SEER (*Surveillance, Epidemiology and End Results*) it is estimated that 3000 new GIST cases should be diagnosed annually in the U.S. The same investigation shows that the gender distribution is 54% men and 46% women [7].

The most common location is the stomach (60%), the jejunum (30%), but they may be found anywhere along the digestive tract [8, 9]. There is also extra-gastrointestinal stromal tumor (E-GIST). The most common location of E-GIST is in the omentum and mesentery (80%), but they can be localized in the pancreas, abdominal wall or pleura as well [10].

The case shown is of a patient carrying a giant stromal tumor of the greater stomach curvature with local invasion, causing surgical tactic problems.

## Case report

We present the case of a 66-year-old male patient. He presents an increased volume of the abdomen, especially in its upper part, weight loss, epigastric pain accompanied by a quick sensation of fullness after meals. All these symptoms appeared three months ago, worsening progressively. Physical examination reveals painful epigastric distension.

Laboratory tests reveal: alanine transaminase (ALT) 110 U/L, aspartate transaminase (AST) 143 U/L, amylase 78 U/L, direct bilirubin 0.24 mg/dL, total bilirubin 0.31 mg/dL, creatine-kinase (CK) 902 U/L, glycemia 93 mg/dL, lactate dehydrogenase (LDH) 527 U/L, International Normalized Ratio (INR) 1.11, white blood cells (WBC) 11.4, hemoglobin 10.6 g/dL, hematocrit (HCT) 31.7%, red blood cells (RBC) $3.58\times10^{12}$/L.

The patient's medical history includes stage II essential arterial hypertension and non-insulin dependent diabetes.

Abdominal ultrasonography shows a tumor with a maximum diameter of 24 cm, heterogeneous, with interior transonic images, which occupies the entire left hypochondrium and comes into intimate contact with the left lobe of the liver and moves the left kidney caudally. The cholecyst had an infundibular gallstone image.

The computerized tomography shows a heterogeneous tumor size 25/22 cm. The formation presents numerous necrosis areas. It is in intimate contact with the left lobe of the liver (on 8.5 cm) and the spleen. It invades the left hemidiaphragm. The starting point is probably the greater stomach curvature. No intra-abdominal adenopathies noted. Gallstone image is revealed (Figure 1).

Surgery is approached with a bi-subcostal laparotomy. Exploration highlights the origin of the tumor in the vertical portion of the greater stomach curvature, with intimate adherences to the left lobe of the liver and the spleen. The left hemidiaphragm shows a tumor invasion (Figure 2).

The extremely hemorrhagic tumor is mobilized. In order to reduce blood loss, a clamp is applied on the greater stomach curvature. The tumor was en-bloc resected, with the adjacent side of the greater stomach curvature and the invaded left hemidiaphragm (Figure 3).

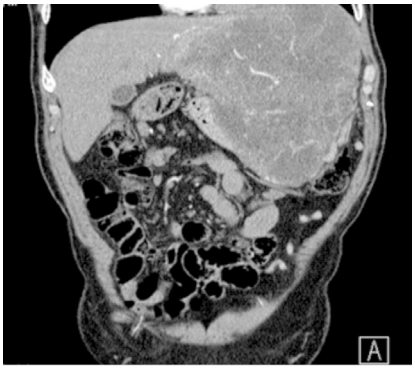

**Figure 1** – ***Computer tomography aspect of the tumor showing the appurtenance of the tumor to the greater curvature of the stomach, its dimension and local invasion in left hepatic lobe and left hemidiaphragm.***

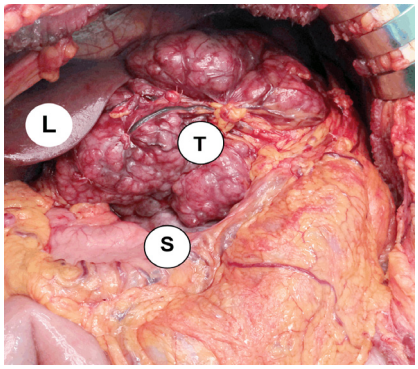


**Figure 2** – ***Preoperative aspect of the tumor (T) with the origin on the greater stomach curvature (S) and intimate adherences to the left lobe of the liver (L).***

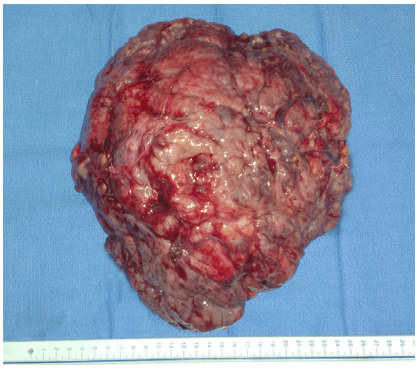

**Figure 3** – ***Specimen after resection with its dimension (25×20×27 cm) and macroscopic aspect with focal areas of hemorrhage necrosis and cysts.***

Surgical recovery was favorable. The gastric suction was suppressed on the fifth day after surgery, with resumption of oral nutrition. The hospital stay has been prolonged by an enterocolitis with *Clostridium difficile*, with a severe dehydration syndrome, requiring the introduction of a parenteral hydration and antibiotics according to the antibiogram, with Vancomycin and Metronidazole. The patient leaves the service after 17 days of hospitalization.

The macroscopic aspect of the tumor showed that it had quite large dimensions (25×20×27 cm), a bosselated aspect, with multiple areas of necrosis and hemorrhage.

For the microscopic study, there were harvested tumoral fragments that were immediately fixed after the surgical excision in 10% neutral formalin solution for 24 hours, subsequently being included in paraffin, using the standard histopathological protocol. The sectioning of the biological material included in paraffin was performed in the Microm HM350 rotary microtome equipped with a system of section transfer on water bath (STS, Microm). For the histological study, there was used the classical staining with Hematoxylin–Eosin (HE).

For the immunohistochemical study, there were performed sections with a 3 μm thickness, which were collected on blades covered with poly-L-Lysine for increasing the adherence of the biological material to the slide blade, after that they were kept in a thermostat $37^0$C for 24 hours. Then, after the deparaffinization and hydration of histological sections, the biological material was incubated for 30 minutes in a 1% hydrogen peroxide solution. The sections were then washed in tap water, and then boiled in a sodium citrate solution (pH 6) for 20 minutes for antigen demasking. After boiling, they were left to cool down for 15 minutes, then they were washed in a phosphate-buffered saline (PBS), followed by the stage of blocking the endogenous peroxidase in 2% free-fat milk for 30 minutes. Then, the sections were incubated with primary antibodies at $4^0$C over night, and the next day the signal was amplified for 30 minutes by using the secondary antibody with polymer support peroxidase, the detection system EnVision, Dako. The signal was detected with 3,3'-diaminobenzidine (DAB) (Dako) and, after the Hematoxylin contrasting, the blades were covered with DPX (Fluka).

For the immunohistochemical study, we used the following markers (Table 1):

**Table 1** – ***Antibodies used for the immunohistochemical analysis***

| Antibody | Code | Clone | Specificity | Antigen retrieval | Dilution | Source |
|---|---|---|---|---|---|---|
| *CD117 (c-kit)* | A4502 | Polyclonal | Interstitial Cajal cells | EDTA, pH 9 | 1:400 | Dako |
| *CD34 class II* | M7165 | QBEnd-10 | Vascular endothelium | Sodium citrate, pH 6 | 1:50 | Dako |
| *Vimentin* | M7165 | V9/Ms, IgG1 | Mesenchymal-derived cells | Sodium citrate, pH 6 | 1:50 | Dako |
| *α-SMA* | M0635 | HHF35, Ms, IgG2a | Myofibroblast | Sodium citrate, pH 6 | 1:50 | Dako |
| *p53* | DO-7 | Ms/Hu/Monoclonal | TP53 | Sodium citrate, pH 6 | 1:50 | Dako |
| *Ki67* | MIB-1 | Ms/Hu/Monoclonal | Cellular proliferation | EDTA, pH 9 | 1:50 | Dako |

The microscopic study, using the classical stainings, showed a tumor made up of fusiform cells covering the entire gastric wall, except for the mucosa, which was not invaded by the tumor (Figure 4). The tumoral cells presented abundant cytoplasm, mildly basophilic, ovalary, normochromic, large dimension nuclei, with obvious nucleoli (Figure 5). The cellular organization was in the form of nodules, with dimensions from a few hundred microns to a few millimeters, separated by finely formed septa of lax conjunctive tissue made of blood vessels. The tumor appeared poorly vascularized, except for the areas of lax conjunctive tissue from these septa where some vessels appeared strongly congested (Figure 6), while others appeared with a discontinuous wall, surrounded by microhemorrhagic areas (Figure 7).

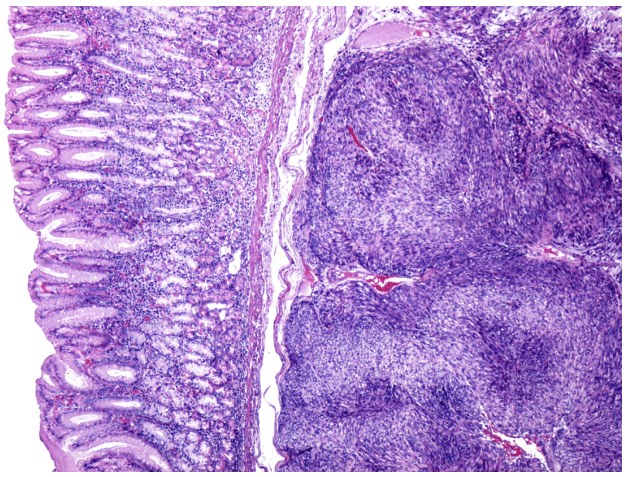

**Figure 4** – ***Overall image of the tumor where we may observe its development in the stomach submucosa and muscles, without any mucosa invasion, by formation of nodules, separated by fine septa of lax conjunctive tissue. HE staining, ×40.***

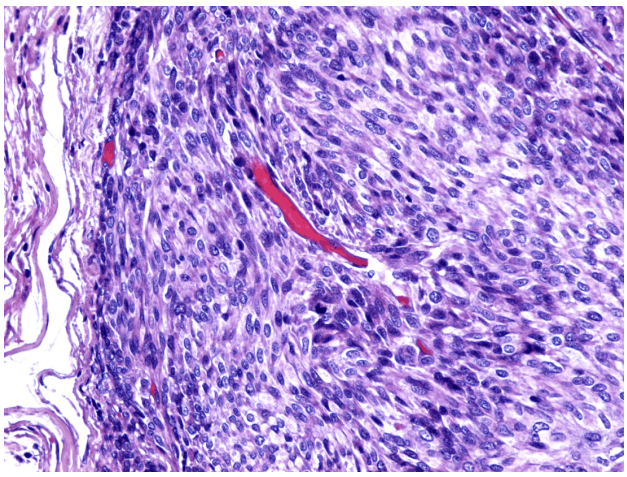

**Figure 5** – ***Tumoral cells with a fusiform aspect, with rich cytoplasm, mildly basophilic and big, hypochromic nuclei. HE staining, ×200.***

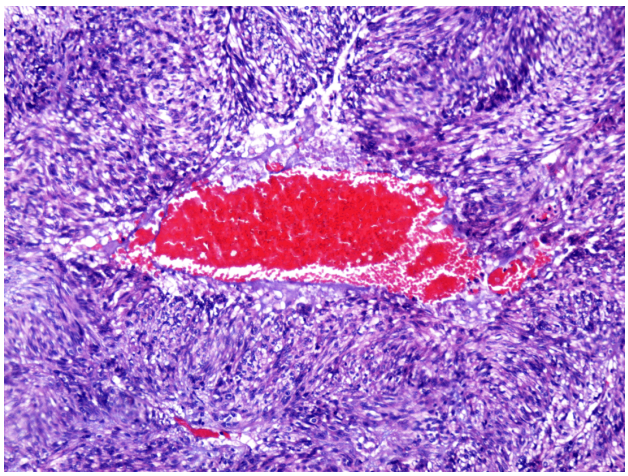

**Figure 6** – ***Conjunctive septa with congested blood vessels. HE staining, ×100.***

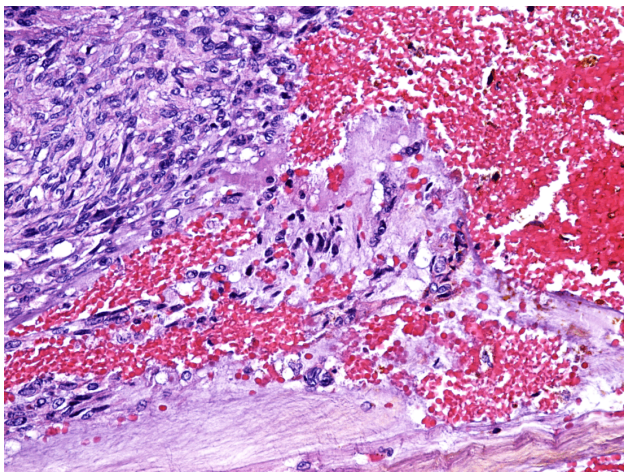

**Figure 7** – ***Tumoral area with altered blood vessels, associated with microhemorrhages. HE staining, ×200.***

For the positive and differential diagnosis, as well as for the estimation of tumoral cell proliferative ability, we used several immunohistochemical markers.

Starting from the histological aspect of the tumor in HE staining, we used the CD117 antibody (c-kit), being known as a specific marker for GIST. CD117, the product of the proto-oncogene c-kit, is expressed in various subsets of hematopoietic stem cells, mastocytes, melanocytes and Cajal interstitial cells in the gastrointestinal tract. As there may be observed from our images (Figure 8, a and b), the reaction of tumoral cells was quite intense to this antibody. The reaction appeared at cytoplasm level in over 95% of the tumoral cells.

CD34 is a frequently used marker in the positive and differential diagnosis of GIST. CD34 is a glycoprotein that facilitates the intercellular adhesion or the cellular adhesion to the stroma. Even though it is a marker of stem and progenitor cells, in tumoral cells, by its phenotype changes, this marker may be a positive one. In our study, this antibody marked over 90% of the tumoral cells (Figure 9, a and b). CD34 was also positive in the endothelium of blood vessels.

Vimentin belongs to the proteins present in the intermediary filaments of mesenchymal cells. In our study, the reaction of stromal tumoral cells was quite intense, over 90% of the cells being positive to vimentin (Figure 10, a and b).

In order to perform a differential diagnosis with the muscular tumors (leiomyoma and leiomyosarcoma), there was evaluated the reaction of tumoral cells to the alpha-smooth muscle actin (α-SMA). The reaction of tumoral cells to α-SMA was quite weak, less than 10% of the tumoral cells inconstantly expressing this marker (Figure 11, a and b).

The evaluation of tumoral cell proliferative activity by using the Ki67 marker showed that mitotic activity was reduced, less than 5% of the tumoral cells being positive (Figure 12). Also, the affectation of p53 protein was practically absent, less than 3% of tumoral cells expressing this immunomarker (Figure 13).

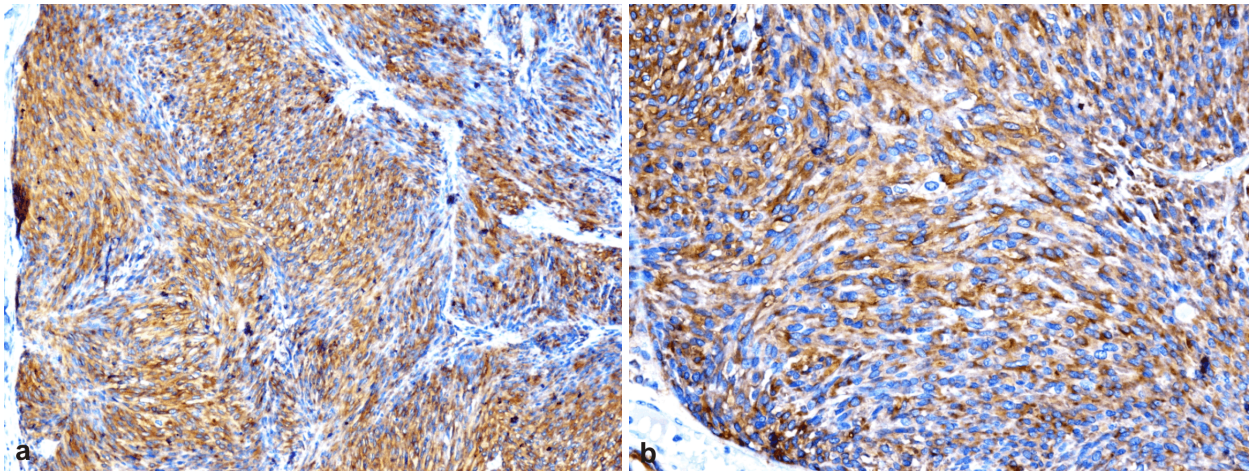


**Figure 8 –** ***(a) Tumoral cells with an intensely positive reaction to CD117. Immunomarking with anti-CD117 antibodies, ×100; (b) Detail from a previous figure where we may observe a positivity in over 90% of the tumoral cells in CD117. Immunomarking with anti-CD117 antibodies, ×200.***

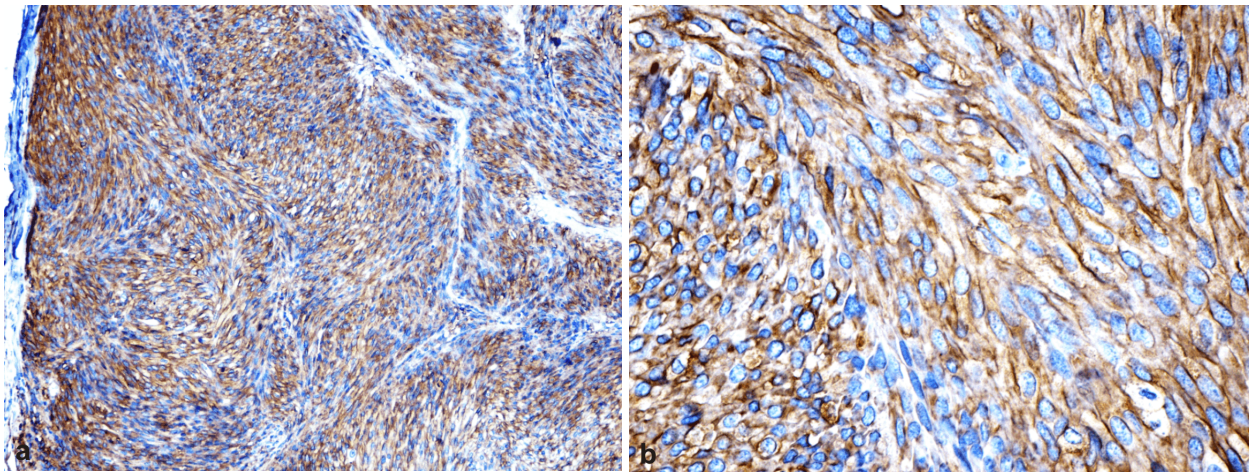


**Figure 9 –** ***(a) Intensely positive reaction of tumoral cells to the CD34 antibody. Immunomarking with anti-CD34 antibodies, ×100; (b) Detail from the previous figure. Immunomarking with anti-CD34 antibodies, ×200.***

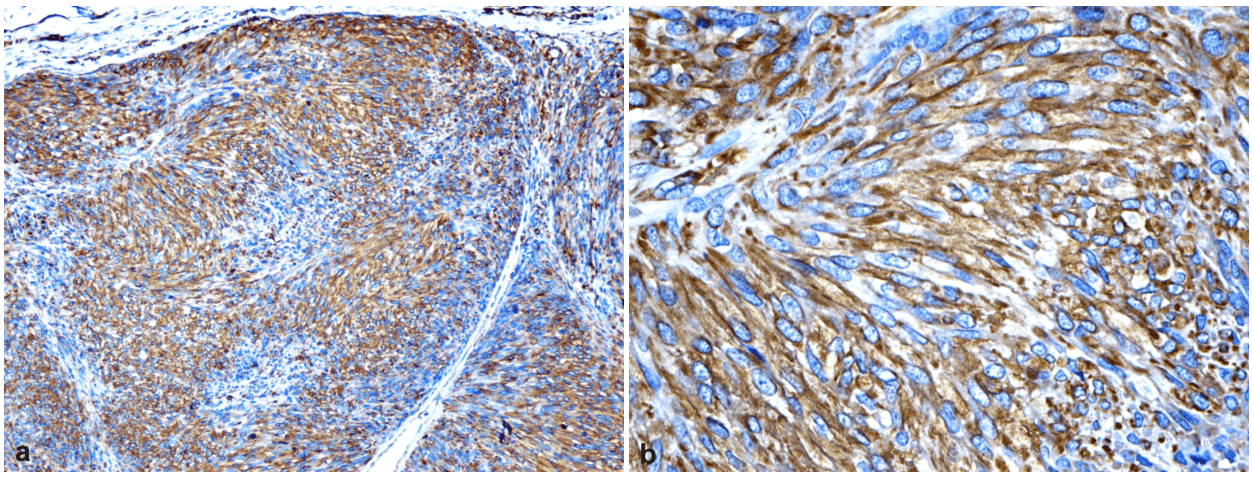


**Figure 10 –** ***(a) Overall image of tumoral cells reaction to vimentin. There may be observed that more than 90% of the cells are intensely positive. Immunomarking with anti-vimentin antibodies, ×40; (b) Fusiform tumoral cells with an intensely reactive cytoplasm to vimentin. Immunomarking with anti-vimentin antibodies, ×200.***

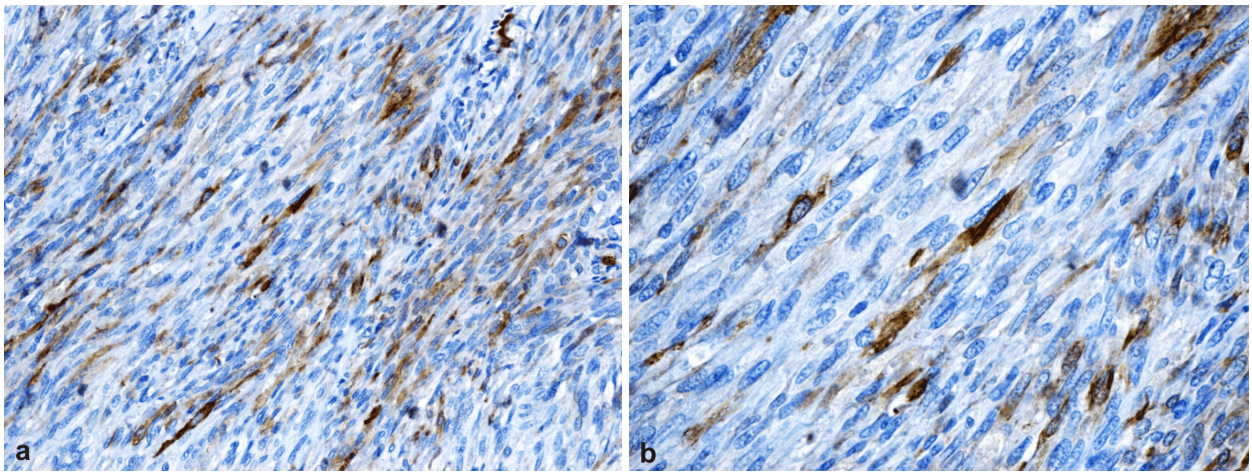


**Figure 11** – ***(a) Tumoral cells with a poorly positive reaction to α-SMA. Immunomarking with anti-α-SMA antibodies, ×100; (b) Detail from the previous figure where we may observe that less than 10% of tumoral cells are positive to α-SMA. Immunomarking with anti-α-SMA antibodies, ×200.***

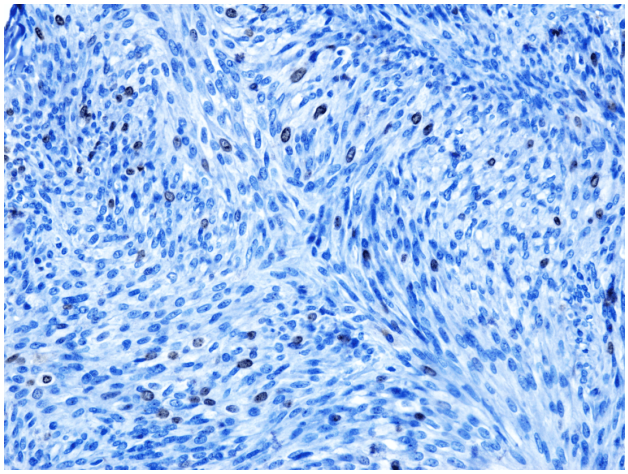

**Figure 12** – ***Tumoral cells with a poorly positive reaction to Ki67, showing a reduced proliferative reaction. Immunomarking with anti-Ki67 antibodies, ×100.***

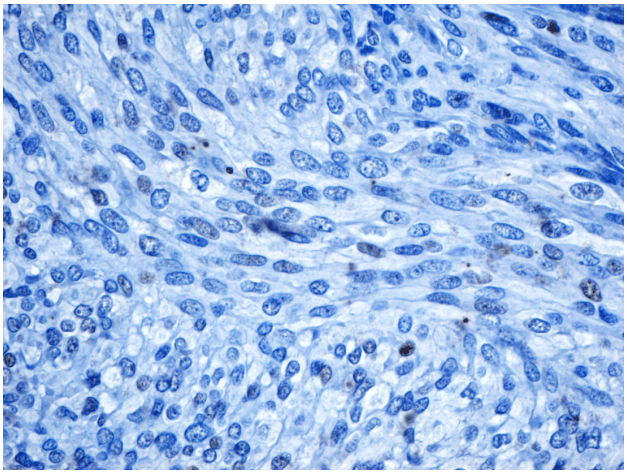

**Figure 13** – ***Tumoral cells with an almost absent reaction to p53, which denotes a lack of TP53 gene alteration. Immunomarking with anti-p53 antibodies, ×200.***

## Discussion

Gastrointestinal stromal tumors are the most common mesenchymal malignancies representing 0.1–3% of gastrointestinal cancers [11, 12]. These tumors are the consequence of a mutation of the Kit gene, which activates the CD117 oncoprotein, which is positively in 90% of the cases and GIST present the Kit expression. In our patient, whose tumor is of gastric origin, the immunohistochemistry is positively diffuse for CD117, CD34 and vimentin. This is in agreement with other authors [13]. On the other hand, CD117 is observe both in spindle cells and epithelioid subtypes of GIST in all locations. These results indicate that CD117 is a specific marker for GIST [14].

α-SMA is less important for the diagnostic of gastric GIST then CD117 and CD34. α-SMA is most frequent in small intestinal GIST and S100 protein is specific for gastrointestinal schwannomas [15]. The prevalence of the male gender and of the age between 60 and 69 years as the maximum incidence of GIST occurrence is found in our patient as well. GIST can occur wherever there are Cajal cells (ICCs – interstitial cells of Cajal), but the gastric localization is the most frequent in 60% of GIST. In this case report, the origin of the tumor is the greater stomach curvature. The GIST symptomatology is approximately non-specific. These accusations are extremely varied, bleeding, intestinal occlusion, perforation [17]. However, 30% remain asymptomatic, being discovered incidentally during surgeries, imagistic examinations or autopsies [17, 18]. Our patient was asymptomatic for a long period of time. When it became manifest, it showed an increase in abdominal volume, diffuse epigastric pains and sub-occlusive phenomena. The diagnosis was made by abdominal ultrasonography and CT scan. The latter was superior, indicating the gastric origin of the tumor, as well as the local invasion. Surgery treatment remains the main GIST treatment. Intra-operatory tumor rupture must be avoided, as it is an important factor in the occurrence of relapse [19]. Lymphatic dissection is not required for GIST witch spread hematogenously mainly [20]. A curative resection is desired [21]. If the surgery is type R, iterative re-interventions have their indication. If the resection is impossible due to local mutilation, a neoadjuvant Imatinib (Gleevec, Novartis Oncology) therapy is recommended [22]. The efficiency of the Imatinib response is evaluated through PET Scan

[1, 9]. In this case, the tumor was extremely large, 25/20/27 cm and intimately adherent to the left lobe of the liver an invading the left hemidiaphragm, with firm consistence and intensely hemorrhagic during mobilization maneuvers. In order to reduce blood loss, a vascular clamp has been placed on the entire vertical portion of the greater stomach curvature. A RO type resection has been carried out, also requiring a partial resection of the left hemidiaphragm [23].

Our patient is placed in the 90% disease progression risk class. To assess the likelihood of disease recurrence in two years, we used the following nomogram [24]. According to this nomogram, our patient has a 90% risk of recurrence two years after the intervention. As in our case, the literature confirms that the most important morphological criterion with a predictive role is the mitotic activity index correlated with the size and the localization of the tumor [25]. Contrary, the expression of CD117 and CD34 is not associated with the risk of GIST recurrence [26]. Given the high risk of disease progression, the patient started an Imatinib adjunctive therapy 30 days after the surgery.

## Conclusions

We describe a case of giant GIST tumor of the stomach. For a long time, despite the extremely large size, it was asymptomatic. Once it became manifest, the symptoms were uncharacteristic. CT scan was accurate in the assessment of the tumor size and the estimation of local invasion. Surgical resection was RO type, confirmed by histological examination and without intra-operatory tumor intrusion. The histological aspect is characterized by proliferation of spindle cells. Immunohistochemical is diffusely positive for CD117, CD34 and vimentin. The most important prognostic factors is the mitotic activity (21/5 $mm^2$) correlate with the size the tumor (25×20×27 cm) and the gastric origin. Given the high-risk of disease progression and recurrence in two years, as well as the diffuse positivity for Kit, an adjunctive Imatinib therapy was begun.

### Conflict of interests

The authors declare that they have no conflict of interests.

### Author contribution

All authors have contributed equally to the present work.

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