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Giant Gastrointestinal Stromal Tumor of the Stomach: Case Report and Literature Review

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ABSTRACT

Although GISTs can occur in any part of the digestive tract, most gastrointestinal stromal tumors (GISTs) are found in the stomach. They are generally asymptomatic but may grow and form large masses. We report the case of a nearly asymptomatic patient with a large tumor (around 25 cm) that was successfully removed, followed by adjuvant treatment with tyrosine kinase inhibitor (TKI).
Key words: stomach, gastrointestinal stromal tumor, case report

INTRODUCTION

Gastrointestinal stromal tumors (GISTs) are non-epithelial tumors of the gastrointestinal tract. These mesenchymal tumors account for only 1% of all primary malignant tumors of the gastrointestinal tract (1). Around 60 to 70% originate in the stomach, with the small intestine the second most affected area (20 to 30%), but the colon and rectum (5%), esophagus (< 5%) and more rarely the omentum, mesentery or retroperitoneum may also be affected, with most tumors at these sites being primary gastric or intestinal metastases (1). Gastric GISTs represent approximately 3% of all gastric tumors, only 10-30% of which are malignant (2). The incidence varies according to geographic area, with a global incidence of between 7 and 15 cases per million people per year (3).

Patients with localized GISTs have a 5-year survival rate of 93%, individuals with locally advanced GISTs 80% and those with metastatic GISTs 55% (4). They are typically found in adults aged 50 years or older, rarely in those younger than 40 and very rarely in children.

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CASE REPORT

A 61-year-old patient presented at a gastroenterology clinic complaining of

abdominal pain in the left epigastrium and hypochondrium that had bothered him for around 3 years and worsened 1 month before. The discomfort increased with food intake. He weighed 220 pounds and reported having lost 15 pounds, which he attributed to the nutritionist-prescribed diet. A physical examination of the abdomen was hampered by the patient´s obesity and palpation raised doubts about whether there was any mass, but the patient experienced pain during deep palpation of the left epigastrium and hypochondrium.

Laboratory tests revealed the following: Hb 13.2 g/dl, Ht 38.5, white blood cells (WBC) 4.7, hemoglobin 14.1, hematocrit 38.5, platelets 191,000, red blood cells 4x1012/L, alanine transaminase (ALT) 27 U/L, aspartate transaminase 32 U/L, direct bilirubin 0.21 mg/dL, total bilirubin 0.7 mg/dL, glycemia 105 mg/dL.

The endoscopy examination showed no signs of a tumor or extrinsic compression, revealing only non-invasive esophagitis and slight hyperemia in the gastric antrum, while biopsies of the antrum and gastric body produced no relevant information.

Ultrasound examination showed a nodular mass with mixed texture measuring around 17 cm at its longest axis.

The patient was submitted to nuclear magnetic resonance of the abdomen, showing an expansive solid voluminous formation with necrotic areas (*fig. 1*), with a small T1-weighted hypersignal compatible with hematic/high protein content in the left hypochondrium, without cleavage planes and in contact with a large gastric curvature measuring 18 x 12 x 15 cm (volume 1.177 cm^3).

Due to the large tumor, it was decided to perform open surgery with a midline incision. A segmental resection of the stomach was made using a stapler. Up-on opening the abdominal cavity, a large pedunculated tumor was observed at the level of the greater curvature of stomach with no filtration of adjacent organs, and no signs of peritoneal carcinomatosis or ascites (*figs. 2* and *3*). The adhesions were detached, the greater omentum was removed from the greater curvature using electrocauterization of the tumor region, and the pedicle tumor was resected with the margin following the greater gastric curve with three 60 mm purple loads. After resection, the lesion measured around 25 cm. The abdominal cavity was then closed.

The specimen received for anatomopathological examination consisted of a stomach segment containing a mass measuring 15.0 x 9.0 cm, centered on the gastric wall (*fig. 4*). A cut section showed the epicenter of the lesion in the muscularis propria of the stomach, with a fasciculated homogeneous cut surface. Additionally, there was a liquefactive necrotic region (approximately 10% of the tumor volume). Histological examination revealed that the lesion had high cellularity, consisting of spindle cells, with cytoplasm containing perinuclear vacuoles and nuclei with moderate atypia, and a high mitotic index - 20 mitoses in 5.0 mm^2, corresponding to 50 high power fields (*fig. 5*). Immunohistochemistry showed lesion positivity for the C-Kit, DOG1 and CD34 markers, and positive Ki-67 in 30% of the neoplastic cells (*fig. 5*). These morphological and immunohistochemical findings confirm the diagnosis of high-grade gastrointestinal stromal tumor (GIST). This case report was written according to the Care Checklist.

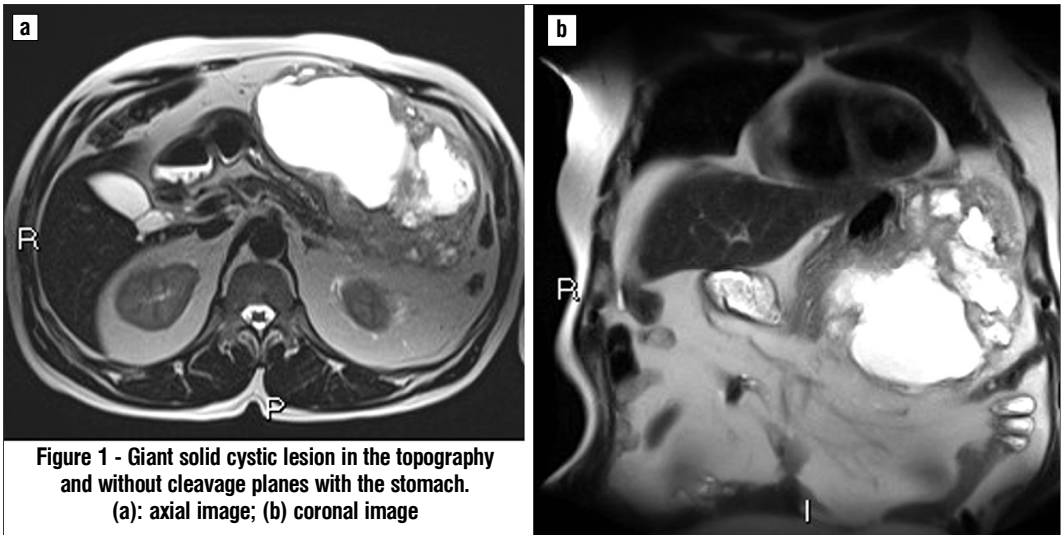

Figure 1 - Giant solid cystic lesion in the topography and without cleavage planes with the stomach. (a): axial image; (b) coronal image

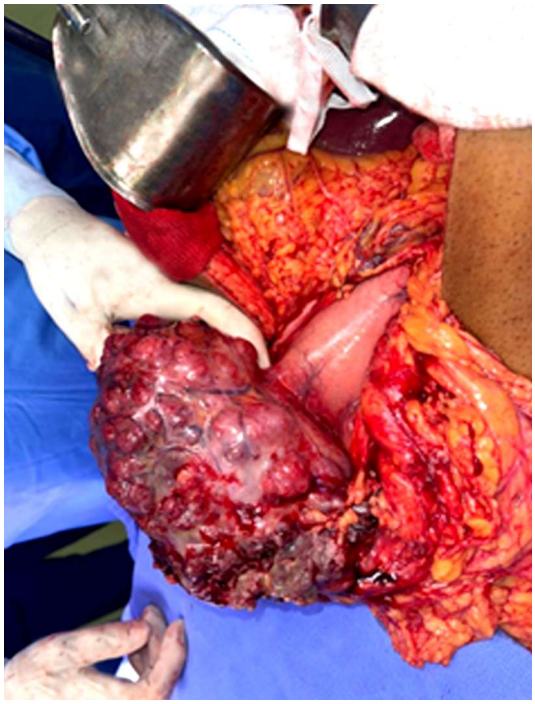

Figure 2 - Lesion in the topography of the greater curvature of the stomach

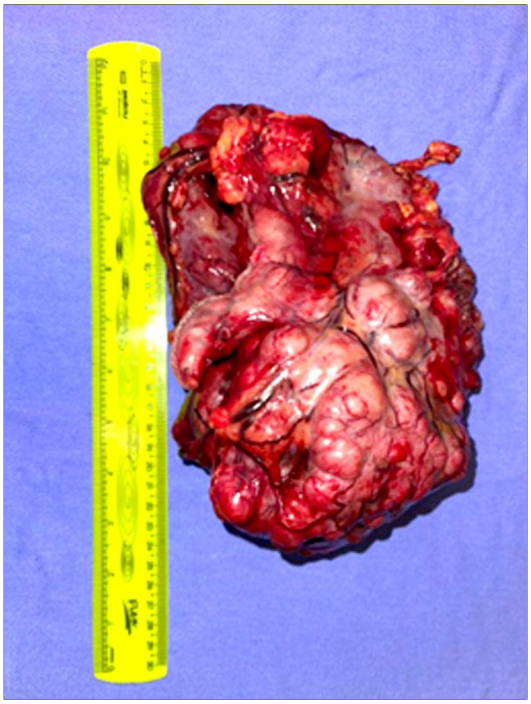

Figure 3 - Tumor after surgical resection

DISCUSSION

GISTs were originally described in 1980 as smooth muscle tumors, but the development of immunohistochemical and molecular diagnostic methods led to assigning them a distinct category.

An important finding was identifying CD117 antigen expression in nearly all GISTs, differentiating them from leiomyosarcomas, leiomyomas and other fusiform cell tumors of the gastrointestinal tract, which are CD117 negative (5).

GISTs originate in the interstitial cells of Cajal (ICC), and are present throughout the gastrointestinal tract, where they function as pacemaker cells to coordinate the peristaltism (6).

It was discovered that the interstitial cells of Cajal (ICC) expressing the c-Kit (CD117), a class III receptor tyrosine kinases for the stem cell growth factor, are the source of GISTs. GISTs develop through gain of function oncogenic mutations in Kit genes or the platelet-derived growth factor receptor (PDGFR), which leads to constitutive activation of receptor tyrosine kinases (6).

The immunohistochemical examination revealed that 95% of GISTs were positive for Kit (CD117) and 70% for CD34 (7). Other markers are DOG-1 (discovered in GIST-1) and the protein kinase C theta (PKC-theta).

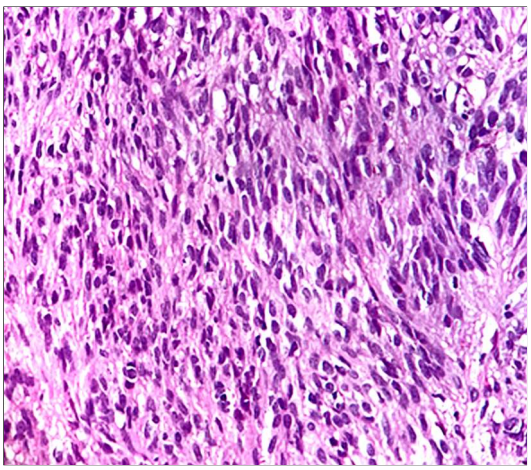

Figure 4 - The lesion has spindle cells, moderate nuclear atypia and perinuclear vacuole. Mitosis can be seen in the upper center. HE, 400x

Microscopically, GISTs may have moderate or high cellularity and are divided into three main types: fusiform (70%), epithelioid (20%) and mixed (10%).

According to Gyvyte et al (10), stage 1 tumors have a low mitotic rate and do not spread to the lymph nodes. Stage 1A tumors are between 2 and 5 cm, while their stage 1B counterparts are between 5 and 10 cm. Stage II tumors have a high mitotic rate, but are 5 cm or smaller with no lymphatic spread. Stage III tumors have

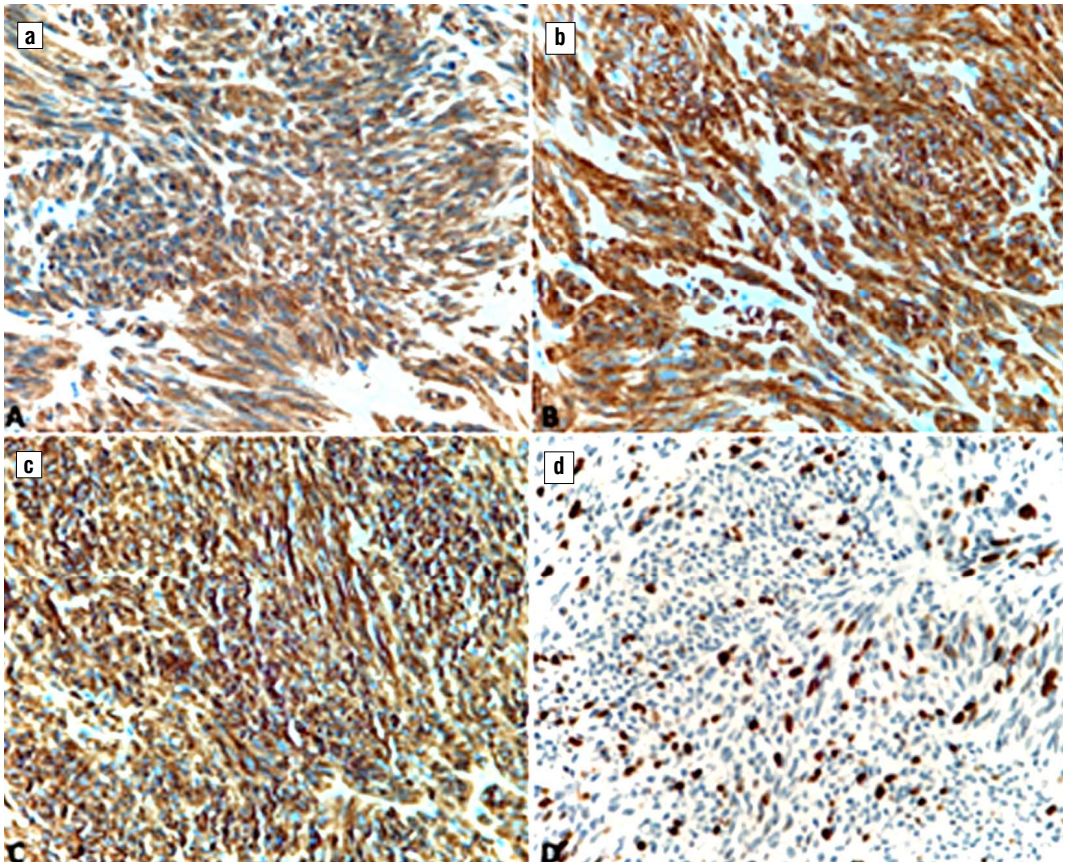

Figure 5 - Immunohistochemistry. (a) C-Kit; (b): DOG1; (c): CD34; (d): Ki-67. 400x

a high mitotic rate, with no lymphatic spread, but are larger than 5 cm in diameter. Stage IIIA tumors are between 5 and 10 cm, while IIIB tumors are larger than 10 cm. Stage IV tumors can be of any size or mitotic rate, but spread to the lymph nodes or distant sites, such as the liver.

Surgery is the therapeutic procedure of choice for patients with primary GIST with no evidence of metastasis, and the objective should be complete resection of the lesion. Laparoscopy can be used for tumors smaller than 5 cm, although successful reports have been described for larger tumors (11). Open surgery is generally indicated for large tumors. The aim of the operation is complete resection with a negative microscopic margin and no bleeding, always taking care not to rupture the tumor capsule (12). Neoadjuvant chemotherapy with tyrosine kinase inhibitor (imatinib) may be indicated for large lesions where the aim is to decrease tumor volume or in cases of metastasis. According to Gyvyte´s classification, our patient was a stage IIIB, that is, tumors larger than 10 cm with no evidence of metastasis. The surgery proceeded with no complications and the patient was discharged on postoperative day 5.

Tumor size and mitotic rate are the pathological characteristics most widely used to stratify GIST risk. In a long-term follow-up of 1765 patients with gastric GISTs, Miettinen et al. reported 86% metastases for tumors >10 cm with mitotic index >5 mitoses/50 HPFs, while same-size tumors metastasized in only 11% of the cases (13).

Adjuvant therapy with imatinib was investigated in a double-blind phase III (14) study (ACOSOG Z9001) that randomized patients with localized primary GIST (≥3 cm) for postoperative administration of 400 mg of imatinib for 1 year or placebo after complete resection. Recurrence-free survival (RFS) was significantly higher when compared to placebo (HR =0.35; 95% CI, 0.22–0.53; P<0.001).

In the two-arm EORTC 62024 study (15), patients with intermediate to high-risk localized resected GIST were randomized for imatinib adjuvant therapy for 2 years versus observation. The results showed increased RFS in favor of the imatinib adjuvant arm (84 vs. 66% in 3 years; 69 vs. 63% in 5 years; log-rank P=0.001).

Another study (16) assessed the role of imatinib

adjuvant treatment for 36 months compared to 12 months in patients with resected GIST with a high risk of recurrence. After median follow-up of 90 months, RFS and overall survival (OS) increased in the 36-month group compared to its 12-month counterpart (5-year RFS: 71.1 vs. 52.3%, respectively; P < .001; 5-year OS: 91.9 vs. 85.3% respectively; P = 0.036).

According to the prognostic classification using tumor size, mitotic index and location, the patient was categorized in the high-risk of recurrence group after surgical resection and indicated for imatinib adjuvant 400 mg/day for 3 years. The patient has been using imatinib 400mg/day for 1 year, with good tolerance and no evidence of disease recurrence.

CONCLUSIONS

In clinical practice, despite being rare, we should always be attentive to the possibility of GIST for large tumors in gastric topography. Surgery is still the procedure of choice for large lesions. Chemotherapy with tyrosine kinase inhibitors plays an important role in preventing recurrence and long-term follow-up is absolutely essential in monitoring possible recurrence.

Author Contributions: Fernando Freire Lisboa conceived the study. Kleyton Santos de Medeiros and Fernando Freire Lisboa designed the study. Fernando Freire Lisboa, Sofia Emerenciano Gurgel, Julião Bezerra, Fábio Medeiros de Azevedo and Carlos Eduardo Pires de Sousa analyzed the case report. Fernando Freire Lisboa, Fábio Medeiros de Azevedo and Carlos Eduardo Pires de Sousa coordinated the discussions and helped in data interpretation. All authors drafted the manuscript, which was then critically revised by all authors. All authors approved the final manuscript.

Conflict of interest

The authors have no conflicts of interest to declare.

Statement of ethics

The study followed the ethical and legal norms recommended by Resolution 466⁄12 of the National Health Council and was approved by the Research Ethics Committee of League Against Cancer (CAAE: 67412423.4.0000.5293).

Written informed consent was obtained from the patient for publication of the details of their medical case and any accompanying images.

Data availability statement

Not applicable.

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