

CYSTIC GASTRIC STROMAL TUMOR NEGATIVE C-KIT*Tumor estromal gástrico cístico c-kit negativo*Leandro C. **BARCHI**, Joaquim **GAMA-RODRIGUES**, Fábio APM **CARVALHO**,
Marcelo C. **BARCHI**, Olivia C. Grimaldi **OLIVEIRA**, Marcelo F. **CARNEIRO**

From the Beneficência Portuguesa Hospital of São Paulo, São Paulo, SP, Brazil.

Correspondence:Joaquim Gama-Rodrigues,
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Accepted for publication: 26/05/2012**INTRODUCTION**

Gastrointestinal stromal tumors (GIST) are rare, representing less than 1% of all gastrointestinal tumors. However, this is the most frequent nonepithelial neoplasm of the digestive tract. Mean age at diagnose is 58 years old, and the two structures usually involved are stomach and bowel¹². The main symptoms are abdominal pain and digestive bleeding², while the most frequent presentation are solid tumors¹¹. Diagnose is confirmed by histology and imunohistochemistry analyses, followed by CD117 analyze which is positive in about 95% of cases⁷. The preferred initial treatment is surgical excision. Recently, the introduction of imatinib mesylate, a monoclonal antibody, has brought great advances in the adjuvant therapy for these patients, especially in tumor control when the primary lesion was locally advanced⁹. This is a case of gastric GIST predominantly cystic with negative c-Kit, but CD-34 positive, successfully treated by laparoscopic surgery.

CASE REPORT

Man of 59 years old, born in Salvador (northeast of Brazil) previously healthy, presented to medical assistance complaining of abdominal discomfort after feeding in the last three months. Denied abdominal pain, heartburn, vomiting, altered bowel habit, gastrointestinal bleeding or weight loss. The abdominal ultrasound showed gallstones and a cystic-solid expansive formation in epigastrium of unknown etiology (Figure 1).

On physical examination the patient was in good general status, well nourished, eupneic, ruddy, anicteric. Vital signs were normal. As for the respiratory

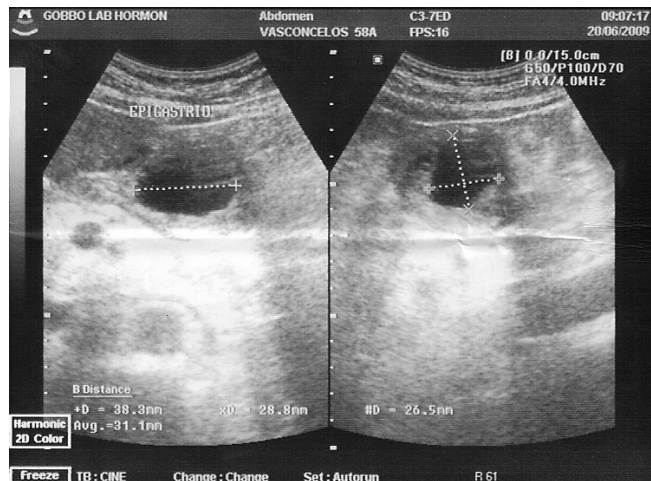


FIGURE 1 - Epigastric solid-cystic lesion with significant central cystic area

and cardiovascular examination no changes were noted. The abdomen was soft, painless to palpation, with bowel sounds present with no visceromegaly. Esophagogastroduodenoscopy, abdominal computed tomography (CT) and serum tumor markers (CA-19.9, CEA and alphafeto protein) were performed. The tumor markers were normal, the Esophagogastroduodenoscopy showed, besides enanthematic pangastritis, two elevated lesions, one located in the submucosa of the posterior wall of gastric antrum, 4 cm in diameter suggesting GIST, and the other in the opposed wall of the antrum measuring 1 cm (Yamada I).

Biopsies of the 1st and 2nd lesions were done, showing only chronic gastritis with follicular hyperplasia; H. pylori was positive in large quantities by Giemsa stain with absence of malignant cells in histology.

The abdominal CT showed, beyond cholelithiasis, a solid-cystic lesion in the gastric antrum, measuring 4.8 x 4.0 cm, with peripheral enhancement after intravenous contrast, wide cystic region liquefied and necrotic, suggesting a gastric GIST (Figure 2).

Once the cystic component was very predominant, an endoscopic ultrasound was done, describing a hypoechoic lesion, irregularly heterogeneous, with a cystic component, thick wall, measuring about 3.9 x 3.1 cm in its greatest diameters, originated in the submucosal layer. Aspiration of 20 ml of turbid liquid and cyst wall biopsies took place; final aspect was of a

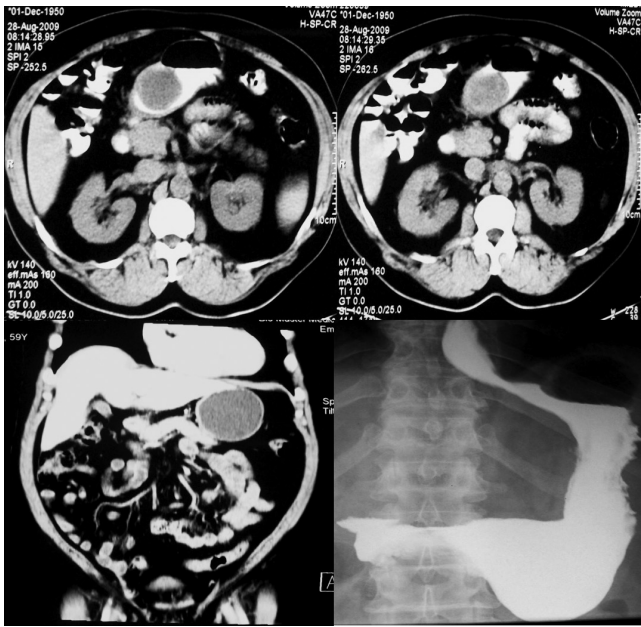


FIGURE 2 - CT scan and serigraphy image with a solid-cystic lesion in the gastric antrum; upper serigraphy of esophagus stomach and duodenum revealed mild effacement of the antrum gastric duplication cyst. The biopsy and fluid analysis were negative for tumor cells.

Serigraphy showed no intrinsic or extrinsic compressions, only with a small effacement of the contrast in the antral region. The patient underwent routine pre-operative tests, cardiac evaluation and eradication of *H. pylori* with amoxicillin, clarithromycin and lansoprasol for seven days.

He was treated with a laparoscopic partial gastrectomy and Billroth II reconstruction using Polya-Reichel's operation technique (end-sided gastrojejunal anastomosis, transmesocolic

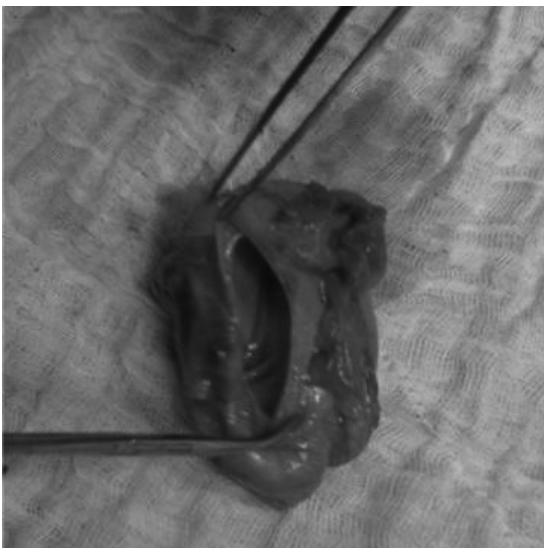


FIGURE 3 - Gastric antrum with cystic lesion with necrotic component in the cyst wall

anisoperistaltic), and cholecystectomy. The specimen consisted of a cystic lesion, thick-walled and there was no second lesion as described in the esophagogastroduodenoscopy (Figure 3). Evolution and follow-up was good at postoperatively.

DISCUSSION

This distinct group of mesenchymal neoplasms consists of spindle cells, with elongated nuclei (present in 70% of cases), epithelioid with abundant cytoplasm and nuclei rounded or pleomorphic and mutation in the tyrosine kinase receptor. The vast majority (95%) had a mutation in gene *Kit*. This gene encodes a membrane receptor with tyrosine kinase activity, recognized immunologically as a CD-117 (*c-Kit*)¹⁵.

The human proto-oncogene *c-Kit* was described by Yarden et al.¹⁵ in 1987, but was Hirota et al.⁸ in 1998 - who curiously did not mention Yarden -, who proposed the origin of GIST in the interstitial cells of Cajal and that the *Kit* mutation would lead to the development of this neoplasm.

The *Kit* is a transmembrane tyrosine kinase receptor and is responsible for various cellular functions, among which proliferation, adhesion, apoptosis and cell differentiation. In GIST the *Kit* gene mutation leads to constitutive activation of *Kit* protein causing an unopposed stimulus for cell proliferation. This leads to tumor development. Most of GISTs that express *c-Kit* positive are also positive for other receptors: CD-34 (70% of cases). A small percentage has no mutation in the *c-Kit*, but in the growth factor receptor derived from alpha platelet (PDGFR α). In GIST, if the expression of *c-Kit* is negative, the PDGFR α positivity is mandatory for diagnostic confirmation.

The DOG1, a monoclonal antibody with no known function, has high specificity and sensitivity for GIST and is strongly expressed on their cell surface. The positivity for DOG1 may aid in the diagnosis of GIST, including mutations at PDGFR α that do not express positive *c-Kit*¹⁴. The expression of DOG1 protein by neoplastic cells of the case confirms diagnosis of GIST, in this clinical and morphological context, which ruled out the need to PDGFR α investigation. In this case, the *c-Kit* was negative, which may occur in only about 5% of cases¹³.

For histological and immunohistochemical diagnosis of GIST, is recommended by the National Institutes of Health (NIH) analysis of CD-117, CD-34, 1A4, desmin, and the Ki-67 antigen (cell proliferation), which does not helps in the diagnosis but influences in prognosis.

Surgery is the treatment of choice, with complete resection of the lesion and with margin free, without the need for lymphadenectomy, because these tumors rarely lead to lymphatic spread. DeMatteo et al.³ in 2000 published a review of 200 cases of GIST, among

them 94 already had metastases at diagnosis. There were only 6% of lymph node involvement in patients with metastatic disease. Miettinen et al.¹² in 2005 published a review of 1765 cases of gastric GIST with a long follow-up and reported "... the fact of GISTs do not develop lymph node metastases avoids lymph node dissection".¹² The lesion must not be enucleated and, if necessary, adjacent organs involved should be removed. Biopsies (pre or intraoperative) should be avoided because it may lead to spread of cancer cells.

In cases of large tumors, unresectable, metastatic or relapsed after surgery (50% cases)^{3,6} therapy of choice has been imatinib mesylate (STI571). This gene therapy inhibits the activity of protein tyrosine kinase Kit by interacting competitively with the ATP binding site in Kit. Without ATP, the source of phosphorus used for kinase function, the Kit molecule cannot phosphorylate the substrate, which inhibits cell proliferation and induces apoptosis. It should be noted that antitumor activity depends on the continuous administration of the drug. The results of more evidence suggest the adjuvant treatment for one year, which produces significant benefit in recurrence-free survival but not overall survival in these patients. There are reports of primary resistance. In these cases it is suggested to bend the daily dose of 400 mg / day to 800 mg or replace the product to the maleate sunitinib (SU11248) another inhibitor of tyrosine kinase¹⁰.

Neoadjuvant imatinib can be applied in some situations to reduce the tumor size and turn initially inoperable cases suitable for surgical treatment. In approximately 70% of cases will be seen reduction in tumor size and disease will become stable at about 15% of cases^{1,4}.

REFERENCES

1. Blanke C, Demetri GD, Mehren M, Heinrich M, Eisenberg B, Fletcher J. Efficacy of imatinib mesylate in advanced gastrointestinal stromal tumor (GIST) patients according to tumor bulk. Proceedings of ASCO Annual Meeting. Abstract 21. 2007
2. Cruz Jr RJ, Glyniadakis N, Cavalcante RN, Cepeda LA, Vincenzi R. Gastrointestinal hemorrhage caused by advanced duodenal gastrointestinal stromal tumor. *Arq Bras Cir Dig.* 20(4):290-2. 2007
3. DeMatteo RP, Lewis JJ, Leung D, Mudan SS, Woodruff JM, Brennan MF. Two hundred gastrointestinal stromal tumors: recurrence patterns and prognostic factors for survival. *Ann Surg.* 231(1):51-8. 2000
4. Eisenberg BL, Judson I. Surgery and imatinib in the management of GIST: emerging approaches to adjuvant and neoadjuvant therapy. *Ann Surg Oncol.* 11(5):465-75. 2004
5. Fletcher CD, Berman JJ, Corless C, Gorstein F, Lasota J, Longley BJ, et al. Diagnosis of gastrointestinal stromal tumors: A consensus approach. *Hum Pathol.* 33(5):459-65. 2002
6. Gress F, Schmitt C, Savides T, Faigel DO, Catalano M, Wassef W, et al. Interobserver agreement for EUS in the evaluation and diagnosis of submucosal masses. *Gastrointest Endosc.* 53(1):71-6. 2001
7. Heinrich MC, Rubin BP, Longley BJ, Fletcher JA. Biology and genetic aspects of gastrointestinal stromal tumors: KIT activation and cytogenetic alterations. *Hum Pathol.* 33(5):484-95. 2002
8. Hirota S, Isozaki K, Moriyama Y, Hashimoto K, Nishida T, Ishiguro S, et al. Gain-of-function mutations of c-kit in human gastrointestinal stromal tumors. *Science.* 279(5350):577-80. 1998
9. Lourenço LG, Caponero R. Adjuvant treatment in GISTs. *Arq Bras Cir Dig.* 24(3):239-41. 2011
10. Maki RG, Fletcher JA, Heinrich MC, Morgan JA, George S, Desai J. Results from a continuation trial of SU11248 in patients with imatinib resistant gastrointestinal stromal tumors (GIST). *Proc Am Soc Clin Oncol.* abstr 9011. 2005
11. Miettinen M, Sarlomo-Rikala M, Sobin LH, Lasota J. Esophageal stromal tumors: a clinicopathologic, immunohistochemical, and molecular genetic study of 17 cases and comparison with esophageal leiomyomas and leiomyosarcomas. *Am J Surg Pathol.* 24(2):211-22. 2000
12. Miettinen M, Sobin LH, Lasota J. Gastrointestinal stromal tumors of the stomach: a clinicopathologic, immunohistochemical, and molecular genetic study of 1765 cases with long-term follow-up. *Am J Surg Pathol.* 29(1):52-68. 2005
13. Ramos MFKP, Zilberstein B, Martins BC, Kondo A, Bresciani CJC, Baba ER, et al. Synchronous gastric GIST and adenocarcinoma: case report and literature review. *Arq Bras Cir Dig.* 20(2):134-6. 2007
14. West RB, Corless CL, Chen X, Rubin BP, Subramanian S, Montgomery K, et al. The novel marker, DOG1, is expressed ubiquitously in gastrointestinal stromal tumors irrespective of KIT or PDGFRA mutation status. *Am J Pathol.* 165(1):107-13. 2004
15. Yarden Y, Kuang WJ, Yang-Feng T, Coussens L, Munemitsu S, Dull TJ, et al. Human proto-oncogene c-kit: a new cell surface receptor tyrosine kinase for an unidentified ligand. *Embo J.* 6(11):3341-51. 1987