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Case Report

Tumors of the Gastrointestinal Stroma. Surgical Management and Tyrosinase Inhibitors (ITK)

Salvador Moreno Galeana[1], Adrián Regalado Aquino[2] and Juan Carlos Rivera Martínez[3]*

[1]*Médico Residente de Cirugía General, Hospital de Especialidades Centro Médico Nacional La Raza, Ciudad de México, Mexico*

[2]*Médico Adscrito al Servicio de Cirugía General, Clínica de Cirugía de Organos Sólidos, Hospital de Especialidades Centro Médico Nacional La Raza, Ciudad de México, Mexico*

[3]*Médico Adscrito al Servicio de Cirugía General, Clínica de Intestino delgado, Hospital de Especialidades Centro Médico Nacional La Raza, Ciudad de México, Mexico*

***Corresponding Author:** Juan Carlos Rivera Martínez, Médico Adscrito al Servicio de Cirugía General, Clínica de Intestino delgado, Hospital de Especialidades Centro Médico Nacional La Raza, Ciudad de México, Mexico.

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Abstract

Gastrointestinal stromal tumors are tumors that can have a benign or malignant behavior. They originate from the interstitial cells of Cajal in the digestive tract. These entities have a slow growth and are recognized as a finding in imaging studies or in the intraoperative as a cause of intestinal occlusion, gastrointestinal bleeding or acute abdomen. Below we present two clinical cases with different presentations. The diagnosis is made with histopathology. Treatment of these tumors is essentially surgical, although it can be completed with targeted molecular therapy.

Keywords: *GIST; Gastrointestinal Stromal Tumors; CD 117; Surgery; Tyrosine Kinase Inhibitors; Treatment*

Introduction

Gastrointestinal stromal tumors (GIST) are the most common mesenchymal neoplasms of the gastrointestinal tract, up to 80% [28]. Other tumors include lipomas, fibromas, neuromas, or angiomas. The incidence of GIST ranges from 10 to 15 cases per million. These tumors are detected as lesions on imaging or endoscopy studies in asymptomatic or mildly symptomatic people or as findings during abdominal surgery [1]. Below we present a series of clinical cases.

Case 1

A 65-year-old female patient attends the Hospital de Especialidades del Centro Médico Nacional (CMN) La Raza, Mexico City, due to oral intolerance. His condition began with diarrheal stools, no mucus or blood, early satiety, abdominal pain in the epigastrium and right hypochondrium, related to food intake; An abdominal ultrasound was performed that reported an anechoic image in liver segments VIII and IV A; A simple abdominal tomography was performed, showing a subhepatic tumor adjacent to the gastric antrum.

TAC with contrast: reported the presence of an image with solid characteristics, isodense in single phase, which upon administration of contrast material shows vascular supply of the gastric arteries, with loss of the interface in the gastric antrum mucosa, exophytic growth, with apparent areas of central necrosis. Findings suggestive of primary gastric mass, suggestive of GIST (Figure 1). A panendoscopy was performed that reported mucosa of the body of the stomach with subepithelial hemorrhage, antrum mucosa with whitish, velvety, raised flat patches that involve all the walls of the antrum.

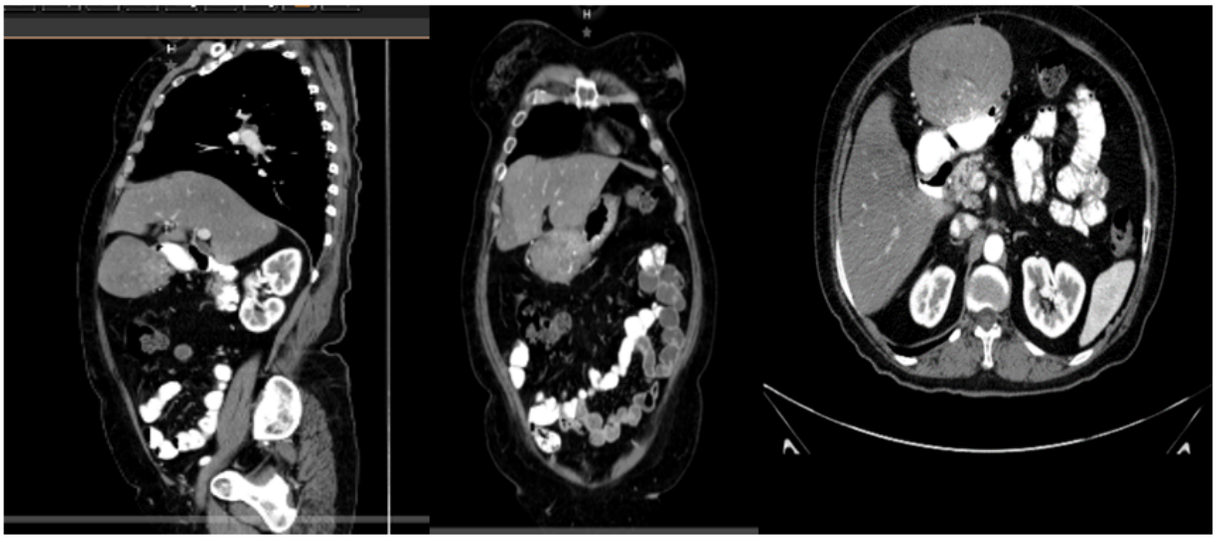

Figure 1: *GIST tumor by CT, sagittal, coronal and axial section. The tumor is subhepatic and comes from the gastric antrum. Image obtained from the HIS system, Hospital de Especialidades del CMN la Raza.*

At the level of the lesser curvature, incisura and anterior wall, a subepithelial lesion measuring 5 x 5 cm is observed. The diagnostic evacuation was completed with endoscopic ultrasound (EUS), which reported a tumor in the location of the body of the stomach towards the greater curvature and anterior face, eroded mucosa, size of the lesion 68 x 79 mm, uninodular shape, rounded and well defined, positive Doppler, lymph nodes a negative distance. A fine needle aspiration biopsy (FNAB) was performed, reporting gastrointestinal stromal tumor (GIST), spindle cell type, expression of DOG-2, CD117 and CD 34, proliferation index < 1%.

Laparotomy was performed with removal of the tumor (Figure 2) with the following findings: pedunculated tumor in the anterior region of the gastric antrum extending into the subhepatic space of 15 x 10 cm with a soft pinkish consistency, removal was performed by means of a stapler. Postoperative patient did not present eventualities, treatment with Imatinib 200 mg PO every 12 hours. She was discharged 5 days after surgery without complications currently.

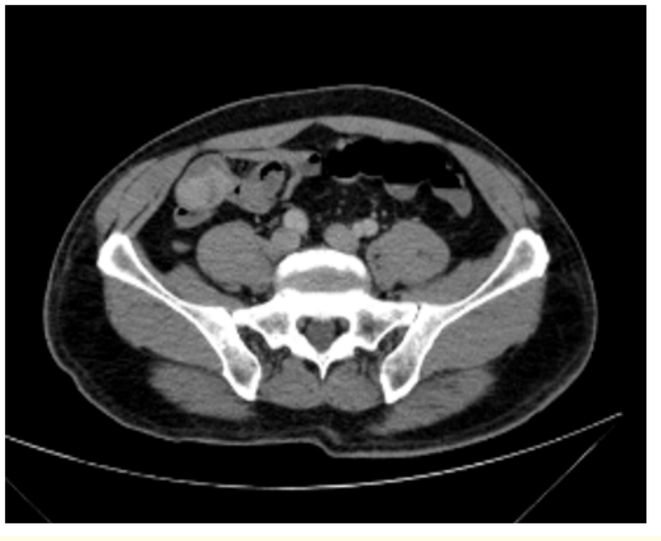

Figure 2: *Surgical specimen. Image of the authors obtained postoperatively at the Hospital de Especialidades del CMN la Raza.*

Case 2

A 56-year-old male patient attended due to digestive tract bleeding. His condition began when he presented diffuse abdominal pain predominantly in the epigastrium, moderate intensity, accompanied by nausea and vomiting of gastrointestinal characteristics on 8 occasions, later adding to the table hematochekic stools with terminal rectal bleeding on 4 occasions. Endoscopy was performed that reported grade A Los Angeles esophagitis and moderate erosive pangastritis. A colonoscopy was also performed because no cause of upper gastrointestinal bleeding was found.

At colonoscopy, he did not report rectal or colon hemorrhage, however, he reported that there was bleeding in 10 cm of the terminal ileum. Therefore, it was concluded as bleeding from the middle digestive tract. A contrasted abdominal CT scan was performed that reported a saccular lesion ending in the cul-de-sac with smooth, well-defined margins of hyperdense content in contrasted phase with attenuation values of 83 UH, dimensions of 32 x 37 x 30 mm in its major axes in relation to a Meckel's diverticulum (Figure 3).

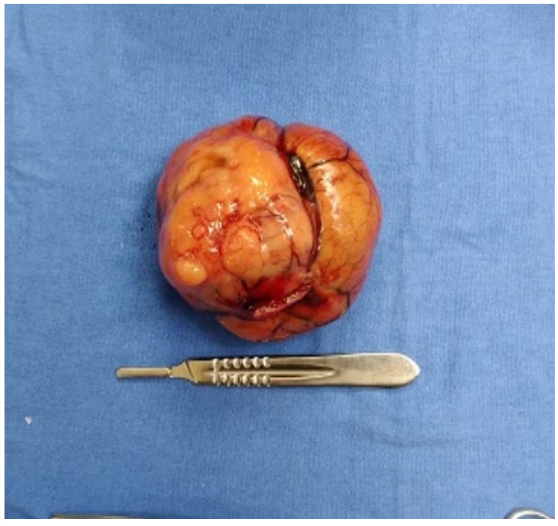

Figure 3: *Axial abdominal CT scan with the presence of a tumor in the small intestine, initially a Meckel's diverticulum was thought, however, a small intestine tumor was found and in the end the pathologist reported a GIST. Which had been the cause of the digestive tract bleeding.*

An exploratory laparotomy was performed with the following findings: Jejunum tumor of approximately 5 x 4 cm lobulated, solid consistency, with abundant vascularization that partially occludes the lumen of the intestine, 4.9 meters from the cecum and 2.2 meters from fixed loop, tumor with margin of 10 cm proximal and distal, a lateral intestinal anastomosis was performed with a stapler. A calcified ganglion was located 10 cm from the lesion in the mesentery. They also reported 3 ascaris lumbricoides in the intestinal lumen of 10 cm long and approximately 2 mm in diameter.

The patient was evaluated by infectology, due to the findings of ascariasis, a single dose of albendazole was given. He was discharged without eventualities 7 days after surgery. The histopathological report was as follows: spindle cell type gastrointestinal stromal tumor - expression of DOG-1, CD117 and CD34, jejunum site, tumor size: 3.2 cm long axis (PT2). Focality: unifocal. Histological grade: G1, low grade. Mitotic index: 1 per 5 mm2. Proliferation index: < 1%. Necrosis: absent. Surgical resection margins: free of injury. Regional lymph nodes: not identified (marginal resection). Evaluation of the risk of recurrence: low risk (4.3%). Regarding the mesentery nodule, it was

concluded as a calcified epiploic appendix. Classification of the pathological stage (PTNM, AJCC 8°): PT2, PNX, PMX, immunohistochemical results: CD117: positive, DOG-1: positive, CD34: positive, ki67: < 1%.

Discussion

Etiology and location

The origin of GISTs are the interstitial cells of Cajal found from the esophagus to the anus. These cells act as pacemakers and regulators of muscle motility in the gastrointestinal tract. Histologically, they are found between the muscularis propria, between myocytes and nerve fibers. They are immunostained with antibodies against CD117 (KIT) [1]. GISTs appear due to a mutation in the c-KIT gene or the platelet-derived growth factor receptor alpha gene [27].

GISTs are distributed as follows: stomach (56%), small intestine (32%), colon and rectum (6%), and esophagus (< 1%). Although they can affect the omentum, mesentery and peritoneum [2]. The most frequent locations of distant metastases are the liver and peritoneum, being found in up to 47% at the time of diagnosis [3]. Pulmonary metastases are uncommon (2%) in the case of GISTs as opposed to soft tissue sarcomas [3]. In the cases mentioned above, the most common locations were stomach and small intestine.

Most GISTs (> 95%) are positive for KIT protein staining (CD117) [1]. Approximately 80% -90% of GISTs carry a mutation in the c-KIT gene (80%) or in the gene platelet-derived growth factor receptor alpha (PDGFRA), which encodes type III receptor tyrosine kinases [4,26].

The tumor affects both sexes equally and the mean age of presentation is between 60 and 70 years of age [1,3]. When GISTs are symptomatic, the clinical picture depends on the location, the size of the tumor and the progression of the disease. In our first clinical case, it was intolerance to the oral route associated with early satiety, while in the second it was gastrointestinal bleeding. In the literature, this last symptom (evident or hidden gastrointestinal bleeding) is referred to as the main manifestation of the disease, even causing shock that may require urgent surgical intervention, as in the second clinical case. The presence of ascariasis in the second patient so far is only an incidental finding, at the moment there is no direct association of ascariasis with GIST in the literature or with any other parasite. Other manifestations of GIST are obstruction (25 - 40%) and perforation [1].

Imaging and endoscopy

Computed tomography (CT) with oral and intravenous contrast is the imaging study of choice for palpable abdominal tumors, gastrointestinal bleeding, or intestinal series with findings of intestinal obstruction. It allows characterizing any abdominal tumor, its relationships with other organs or viscera, assessing its vascularity and the presence of metastases. Magnetic resonance imaging (MRI) has a diagnostic performance comparable to CT and the advantage of not having ionizing radiation; however, CT is the preferred initial imaging study for the detection and staging of the disease. Magnetic resonance imaging could be indicated in patients allergic to contrast (iodine), children and pregnant women [1].

The typical characteristic images of these tumors in imaging studies are: the presence of a solid tumor with a smooth contour that is enhanced with intravenous contrast in the case of CT, vasculature from the wall of the viscera, exophytic growth, central necrosis, sometimes with bleeding or degenerative components [1].

In the case of endoscopy, a submucosal tumor with smooth edges is observed, with a smooth mucosal surface, although it is rare but there may be a central ulcer. This finding is not pathognomonic because it may be another etiology such as a lipoma, leiomyoma, fibroma, or extrinsic compression of another structure or tumor. If there is an ulcer, malignancy such as adenocarcinoma or lymphoma must be ruled out. Simple endoscopy lacks the ability to accurately distinguish between intramural and extramural tumors. Therefore, it must be

complemented with endoscopic ultrasound (EUS), which also allows obtaining biopsies of intramural tumors (by fine needle aspiration, (FNAB), or submucosal endoscopic section or endoscopic resection with a loop, although they would imply a risk of perforation and hemorrhage) and assesses the presence of lymph node growths in the area adjacent to the tumor and, if possible, biopsy these. By EUS, GISTs are hypoechoic and present as homogeneous lesions with well-defined margins, although there are a small number of described tumor cases of tumors that may have irregular margins and ulcerations [1].

Treatment

The only curative treatment in GIST is surgery, as long as the GIST is resectable. Curative surgery is considered to be one that presents microscopic negative surgical margins (R0) and tumor removed without rupture of its tumor pseudocapsule; wide margins have no benefit in disease control [3,27].

Conservative surgery should be the procedure of choice due to the local infiltrative behavior of GIST [1]. Lymphadenectomy is not necessary because lymphatic involvement is rare except in pediatric patients [14]. However, trans-surgical revision of the liver and parietal peritoneum is important for Objective possible metastasis. Despite the above, up to 40% - 50% of patients who have undergone optimal surgery may experience tumor recurrence [1,14]. The treatment of GIST < 2 cm is controversial; although active monitoring of the lesion could be an option, surgery will always be the choice because there are no data on growth behavior and metastatic potential of lesions smaller than 2 cm, although each case must be individualized taking into account takes into account the surgical risk of the patient, his comorbidities and his decision [15,27].

In our cases, we opted to indicate imatinib in the first patient due to the size of the tumor greater than 10 cm (high risk). While the second case was not indicated due to low risk (size of 3.2 cm and mitotic index of 1 per 50 CAP).

In high-risk patients, in a US trial called ACOSOG Z9000 of 106 patients treated with imatinib 400 mg orally every 12 hours, overall survival at 1, 2 and 3 years is 99%, 97%, and 83%, respectively. And the recurrence-free survival at one, two, and three years was 96%, 60%, and 40%, respectively [24].

Conclusion

Gastrointestinal stromal tumors must be met with multiple differential diagnoses due to their atypical presentation that can mimic any intramural tumor of the gastrointestinal tract from the esophagus to the anus. The surgeon will deal with this neoplasm in a wide range of manifestations from asymptomatic patients, patients with dysphagia, with intestinal obstruction with gastrointestinal bleeding or with visceral perforation. These tumors can have a benign or malignant behavior. Timely detection is paramount.

The only curative treatment is surgery. Fortunately, surgery can be conservative and without lymphatic dissection. On the other hand, these tumors are a clear example that the treatment directed against cellular enzymes is the perspective of the future.

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