An incidental finding of a gastrointestinal stromal tumor (GIST) in the stomach following laparotomy: case report and literature review

Mauricio Melo Peñaloza, MD,1 Dolly Williamson,2 Lady Vargas.2

INTRODUCTION

GISTs are neoplasms that arise from the gastrointestinal mesenchymal stroma. GISTs probably originate in totipotent stem cells which also form interstitial cells of Cajal (ICC) which are the gastrointestinal pacemakers of Auerbach’s plexus that activate smooth muscle function through autonomic neural modulation. These stem cells differentiate into cell groups that do not express smooth muscle markers like desmin and actin. GISTs represent 1% to 2% of all gastric neoplasms and nearly 30% of them are potentially malignant (2, 6, 33).

The first recorded use of the term GIST was by Mazur and Clark in 1983. They used it to designate non-epithelial tumors of the gastrointestinal tract which lacked ultrastructural patterns of smooth muscle but which also had unexpected neural markers closely related to ICCs which were detected by immunohistochemistry techniques. Mazur and Clark initially proposed the term “stromal tumors”, but the term was later modified to “gastrointestinal stromal tumors” (3, 4, 5, 18, 19, 20).

In 1998, Hirota et al. showed that the presence of the c-KIT proto-oncogene, a tyrosine kinase III receptor, was required for the normal development of ICCs. The human genome has about 90 tyrosine kinase (TK) receptors and 43 genes associated with them. Their products regulate cell proliferation, survival, differentiation, function and motility. The C-Kit gene is localized in chromosome 4 and codes for a transmembrane TK type III receptor which is also called KIT (CD 117 antigen). They are expressed by ICCs. More than 90% of GISTs and ICCs express the KIT receptor (c-KIT).

Morphological studies and immunohistochemistry staining are used for histological identification of these tumors. Macroscopically, GISTs are structures that range from few millimeters across to many centimeters in diameter. Some of these tumors are more than 30 cm wide. They can be diffuse, encapsulated or multinodular. When they are cut, they seem fibrous with areas of hemorrhaging, cystic degeneration and central necrosis. GISTs are often intramural tumors and usually compromise the submucosal and mus-
cularis propria layers. Microscopically seventy percent of cases are fusiform, 20% are epithelioid cells, and the rest are mixed cell types. Less than 5% of cases have marked cellular polymorphisms (12).

Immunohistochemistry determination uses many antibodies including monoclonal and polyclonal antibodies able to detect CD117 epitope localized in the external domain of the oncoprotein. The most frequently used is the pAbA4502 (DakoCytomation) (11, 12).

The most common localizations of GIST are in the stomach (60% to 70%), small intestine (20% to 25%) and colon (5%). Approximately 20% of GISTs are small and asymptomatic and are discovered as incidental findings. Their incidence peaks between the ages of 50 and 80 years, with no differences between men and women (1).

**CLINICAL CASE**

On October 16, 2012 a 57 year-old woman who had had a cholecystectomy performed on October 6, 2012 came to the emergency room of the departmental hospital of Villavicencio, Meta. She had nausea, abdominal distention and fever. Her surgical wound was hot, swollen and red and was oozing a purulent discharge. She was examined by a general surgeon who initially started antibiotics. On the second day of treatment he decided to perform a laparotomy to drain the abscessed hemoperitoneum. The day after surgery the patient presented coffee grounds emesis, diarrhea, melena and pain in the upper abdominal hemisphere. An endoscopy showed an epithelial mass of 6 cm diameter which was compatible with GIST. It had eroded areas and stigmas of recent bleeding located in the posterior proximal third of the mucosa of the fundus 6 cm distal from esophagogastric junction (Figure 1).

An abdominal CAT scan showed the lesion in the location described above (Figure 2). During surgery a tumor mass was found in the posterior fundus of the stomach. The lesion was resected with wide margins and the material was sent to pathology.

Macroscopic pathology findings showed a mass with a smooth brilliant brownish-grey surface that weighed 42 grams and measured 8 cm x 4 cm x 2 cm. Vascular markings could be seen on its exterior surface. When cut its interior was whitish with areas of hemorrhaging. One border had brownish-grey friable content. Cuts 1 to 3 produced microscopic findings with four areas of friable content, a mitotic count of 1 per 50 high power fields (HPF). A fragment of the greater omentum that measured 12 cm x 5 cm x 1 cm had areas free of congestive tumor. Immunohistochemistry studies reported positively for CD117, S100, and focal CD34 with smooth muscle actin. It also showed a high rate of cell proliferation with Ki167 at 1% (Figure 3 and 4). There was no clear description of the lesion’s edges.

The patient was discharged and treatment with 400mg of orally administered Imatinib once in day was initiated. Three months later a follow up examination using endoscopic ultrasound showed a hypoechoic homogeneous lesion in the cardia. It measured 12.6 mm x 6.9 mm and was in the 4th hypoechoic layer which is the muscularis propria. This is compatible with GIST. The patient is currently being monitored and treated with 400mg Imatinib once a day. She has responded favorably to treatment and was examined with...
endoscopic ultrasound again on April 5, 2013 at which time a biopsy of the lesion in the fundus was performed.

**Figure 3.** Immunohistochemical staining of the GIST of the stomach.

**Figure 4.** Immunohistochemical staining of the GIST of stomach.

**DISCUSSION**

Since the biological behavior of GISTs cannot usually be predicted easily, it is difficult to classify them. The most important prognostic morphological factors are the mitotic count and the size of the tumor which are related to progression of the disease. Hence, use of the terms *prognostic* and *risk group* is better than *benign* and *malignant* lesion.

In our case, we employed the Fletcher risk table (2002) as modified in 2006 on the basis of the Miettienen and Lasota surveys (16, 23, 29, 36, 40). The classification has two categories according to the mitotic rate and seven categories according to tumor size: the greater the mitotic rate and tumor size, the greater the risk of tumor progression (Table 1). The tumor described in this article had a low risk of progression because its mitotic count was 1 in 50 high power fields and its dimensions were 8cm x 4cm x 2 cm.

It has also been proposed that a positive result for Ki67 is an indicator of GIST and that when more than 10% of nuclei tint positively for Ki67 it is an indicator of metastasis. In this instance, the tumor had a Ki67 index of 1% (23, 24, 29).

**Table 1.** Primary stomach and small intestine GIST risk stratification.

<table>
<thead>
<tr>
<th>Mitotic index</th>
<th>Tumor size (cm)</th>
<th>Stomach progression risk</th>
<th>Small intestine progression risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 5 per 50 HPF</td>
<td>&lt; 2</td>
<td>Very low</td>
<td>Very low</td>
</tr>
<tr>
<td></td>
<td>&gt; 2 and &lt; 5</td>
<td>Very low</td>
<td>Very low</td>
</tr>
<tr>
<td></td>
<td>&gt; 5 and &lt; 10</td>
<td>Low</td>
<td>Medium</td>
</tr>
<tr>
<td>&gt; 5 per 50 HPF</td>
<td>&lt; 2</td>
<td>Very low</td>
<td>Medium</td>
</tr>
<tr>
<td></td>
<td>&gt; 2 and &lt; 5</td>
<td>Medium</td>
<td>High</td>
</tr>
<tr>
<td></td>
<td>&gt; 5 and &lt; 10</td>
<td>High</td>
<td>High</td>
</tr>
<tr>
<td></td>
<td>&gt; 10</td>
<td>High</td>
<td>High</td>
</tr>
</tbody>
</table>

Subepithelial lesions, often seen in upper endoscopies, have an estimated incidence for 0.3%. Lipomas, vascular structures, cysts, pancreatic remains and extramural structures are included in this category. One of every five subepithelial lesions is a neoplasm such as a GIST. Diagnosis is difficult (17%), even when jumbo forceps are used for biopsies. The diagnostic procedure of choice for submucosal tumors is endoscopic ultrasound because it differentiates between lesions in the gastrointestinal wall lesions and extrinsic compressions and because it also determines the layer of origin and the size and presence of adenopathies with a sensitivity of 64% to 80% (38).

Ulceration of the mucosa occurs frequently in both benign and malignant GISTs. Ulceration has no predictive value but may be related to tumor size. In our case, the symptom that suggested an endoscopic evaluation was gastrointestinal bleeding. We found an 8 cm diameter tumor with multiple superficial erosions indicating a relationship between size and bleeding.

Surgery is still the preferred method of managing this neoplasm. Ideally, the entire tumor can be resected without rupturing it or its pseudocapsule with microscopic tumor free margins. The importance of establishing whether or not the surgical margin contains any tumor lies in the fact that taken together with tumor size and the presence or absence of bleeding it can help determine the prognosis of the GIST and its response to Imatinib (22, 39). In this case, the tumor was 8 cm and there were signs of bleeding, but the pathology of the resected borders was not clear.

In general, the 5-year survival rate for patients with partially resected tumors is between 28% and 35%.

Given the risk of invasion to nearby structures with locally advanced GISTs, neoadjuvant therapy with tyrosine kinase inhibitors is indicated. Once the maximum response from the tumor has been obtained, it is necessary to determine the possibility of surgical resection (22, 41).
Imatinib is a competitive inhibitor of ATP which binds to the tyrosine kinase domain. It inhibits activation and phosphorylation of this domain thereby delaying tumor growth.

The first description of the use of Imatinib (2001) was in the treatment of a woman with a progressively metastasizing tumor that recurred after she had undergone surgery and chemotherapy. The size of the tumor was reduced by 50% in the first two months of treatment, and by 78% after eighteen months. A CAT scan taken four weeks after treatment began showed a significant decrease in the tumor’s glucose uptake. The spread of the use of Imatinib for GISTs after this first description has been one of the most rapid in the history of oncological treatments.

The ideal duration of treatment is still unknown. Some authors recommend lifelong treatment (17, 21). The main adverse effects of Imatinib are periorbital swelling (74%), nausea (52%), diarrhea (45%), myalgia and rheumatic pain (40%) and headaches (26%). Nevertheless, treatment is discontinued in only 7% of all cases because of adverse effect (31).

One study of 106 cases established that Imatinib use is successful when GIST is totally eradicated, but its utility is uncertain for high risk GISTs (26, 32).

The clinical practice guidelines of the National Comprehensive Cancer Network (NCCN) suggest that Imatinib be used after surgery for at least 36 months in patients with high risk GISTs (tumor size > 5 cm and high mitotic index >5 mitosis/50 HPF) (41).

**CONCLUSIONS**

1. The case reviewed was a GIST of the stomach which is its most frequent location.
2. The patient became symptomatic after a complicated cholecystectomy.
3. The main symptom of this GIST was upper gastrointestinal bleeding which has been associated with greater tumor size and poorer therapeutic response.
4. Non-radical surgery was performed but the margins were not reported in the pathology report. Consequently, the patient will need close follow up to prevent dissemination of the neoplasm which has been described in the literature for partial tumor resections with positive margins.
5. The patient received Imatinib mesylate, a drug that has demonstrated its utility for metastasizing lesions. This could eventually improve the long term prognosis for this case because this tumor presented a medium risk of progression according to pathology, Fletcher classification and presence of bleeding.
6. A follow-up endoscopic ultrasound examination found a second lesion of smaller size which could represent short term metastasis.

**REFERENCES**

7. Toro J, Vasquez I, Madrid J. Tumores del estroma gastrointestinal (GIST): papel del cirujano en la era de la medicina molecular.Abr,26-2010,Facultad de Medicina Universidad de Antioquia iatreia@medicina.udea.edu.co


