Gastrointestinal stromal tumors – a retrospective study of 43 cases

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ABSTRACT

Background: gastrointestinal stromal tumors (GISTs) are rare (10 to 20/million). They exist in the whole digestive system and its surroundings, and are most common in the stomach (70%), followed by the small intestine (20-25%), colon and rectum (5%), and esophagus (< 5%). Their clinical presentation varies from small, incidentally found nodules to large and aggressive tumors. Nowadays GISTs are classified according to Fletcher’s classification.

Objective: to review the features of our GIST population.

Methods: a retrospective study of GIST patients identified by immunohistochemical criteria, from 1997 to December 2007, and classified according to Fletcher’s criteria.

Results: 43 patients were included (24 men, 19 women) with a mean age of 62.7 years. Gastric GISTs (20 cases, 46.5%), small intestine GISTs (18 cases, 41.9%); in 5 cases metastases of occult tumors were found. Eighteen cases had no symptoms. Tumors were classified according to Fletcher’s criteria as high-risk (n = 19), intermediate-risk (n = 7), low-risk (n = 12), and indeterminate-risk (n = 5). Death occurred in 10 patients, and 13 patients had metastatic disease.

Conclusions: our results are in accordance with the world literature, in which a majority of cases are men with gastric tumors. The 5-year survival rate was 42%. Fletcher’s criteria were easily applicable criteria and could predict tumor behavior.

Key words: Gastrointestinal stromal tumour. Fletcher’s Criteria. Imatinib. KIT. Leiomyomas.

RESUMEN

Introducción: los tumores del estroma gastrointestinal (GIST) son poco frecuentes, con una incidencia de 10 a 20 casos por millón de habitantes y año. Aparecen en todo el tubo digestivo, mesenterio o epíplón adyacente; siendo más frecuentes en el estómago (60-70%); también pueden aparecer en el intestino delgado (20-25%), colon y recto (5%) y esófago (< 5%). Su presentación varía desde pequeños nódulos asintomáticos hasta formas más agresivas. Su clasificación se realiza actualmente basada en los criterios de Fletcher.

Objetivo: revisión y caracterización de los casos de GIST observados en nuestro centro durante un periodo de 10 años.

Métodos: estudio retrospectivo de pacientes diagnosticados con GIST (identificados por criterios inmunohistoquímicos) desde enero de 1997 hasta diciembre de 2007 y clasificados por los criterios de Fletcher.

Resultados: se estudiaron 43 pacientes (24 hombres y 19 mujeres), con una edad media de 62,7 años. La mayoría de los GIST encontrados se localizaban en el estómago (n = 20, 46,5%), intestino delgado (n = 18, 41,9%) y en 5 casos se detectaron como metástasis de un tumor oculto. Dieciocho casos fueron asintomáticos. Por los criterios de Fletcher 19 eran casos de alto riesgo, 7 de intermedio, 12 de bajo riesgo y 5 casos se detectaron como metástasis de un tumor oculto. Y los pacientes fallecieron por progresión de la enfermedad y 13 pacientes presentaron metástasis a distancia.

Conclusiones: en nuestra serie, tal como en la literatura, se observa un predominio del sexo masculino y mayor frecuencia de localización gástrica. La supervivencia fue del 42% a los 5 años. La aplicación de los criterios de Fletcher fue consistente con la evolución.

Palabras clave: Tumores estroma gastrointestinal. Criterios de Fletcher. Imatinib. KIT. Leiomiomas.

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INTRODUCTION

Gastrointestinal stromal tumors (GISTs) are rare (varying from 0.1% of malignancies in the colon to 13.9% in the stomach) but are the most common mesenchymal neoplasm of the digestive tract (DT) (1-4). In the 1970s, they were thought to originate in smooth muscle cells, being so classified as leiomyomas or leiomyosarcomas (2,4). In 1983, due to electronic microscopy and immunohistochemistry, it became clear that they were an independent group of lesions; Mazur and Clark first classified these mesenchymal tumors as “gastrointestinal stromal tumors” (2,4).

GISTs are defined as spindle-cell, epithelioid and occasionally pleomorphic mesenchymal tumors arising in the digestive tract (1,4), with a suggested origin in the interstitial cells of Cajal or in their stem cells, which are present in the gut wall (4).

GISTs’ immunohistochemical features started with vimentin positivity. Then, in the 1980s it was found that the anti-CD34 antibody was positive in a majority of these tumors (around 70%). Sometime later other positive antibodies were also found, like actin (20-30%), S100-protein (10%), and desmin (< 5%) (4-6). Finally, at the end of the 1990s, a marker that was expressed in more than 90% of tumors was obtained – CD117 (c-KIT). The latter is almost a sine qua non feature for the diagnosis of GIST. (2,4-6).

The KIT protein (CD 117) is a transmembrane type-III tyrosine-kinase receptor whose ligand is a stem-cell factor (2,4). This protein is also present in mast cells, hematopoietic stem cells, melanocytes, germ cells, mammary ductal epithelia, angiosarcomas, melanomas, and seminomas (4). Around 90% of GISTs have KIT mutations (2,3). For the remaining tumors that do not show detectable KIT mutations an alternative mutated gene could be searched — platelet-derived growth factor receptor alpha (PDGFRA), first described in 2003 (2,3).

In 2002, a macroscopic and histological classification was developed (Table I) by Fletcher et al. that divided GISTs into 4 malignancy classes, based on the risk of metastatic disease (7).

OBJECTIVES

Considering recent immunohistochemical discoveries and the various changes occurred in the last years in the diagnosis and clinical approach of GIST, the aim of our study was to identify all clinical cases of GIST diagnosed in our population, to review their features, and to reclassify them according to new categorizations.

MATERIAL AND METHODS

This retrospective study included patients diagnosed with GIST, submucosal lesions or leiomyomas identified by immunohistochemical criteria from January 1997 to December 2007.

The histological sections that were reviewed were representative of lesions and stained with hematoxylin-eosin. All samples were once again evaluated for their cellularity and mitotic count, and reclassified according to Fletcher’s criteria (Table I). Small leiomyomas from the muscularis mucosa were excluded.

For each patient a demographic evaluation was performed. Clinical profile and follow-up after diagnosis and treatment were also assessed by consulting medical records or patients themselves.

Tumor samples were evaluated using immunohistochemical antibodies against CD117, CD34, vimentin (especially for CD117-negative cases), actin, and S100-protein (Dako® or Novocast®). Cases that were CD117-negative were studied by electronic microscopy to exclude those which were structurally incompatible with a diagnosis of GIST.

In 10 patients a study for KIT mutation (exons 9,11,13,17) was performed. Inclusion criteria were: young age (15 years old) and severe disease (high-risk disease according to Fletcher’s criteria or metastatic disease). No study of PDGFRA mutations was performed.

RESULTS

Forty-three patients were included: 24 men, 19 women, mean age: 62.7 years (18 to 86 years), whose features are described in Table II.

All tumors were firstly identified in macroscopic surgical pieces, except for one that was first diagnosed in an endoscopic biopsy and submitted to surgery later on. Nine surgical pieces had invaded margins.

Immunohistochemical evaluations revealed the expression of CD117 in 37 tumors (86%), CD34 in 22 (51.2%), vimentin in 12 (27.9%), actin in 7 (16.3%) and desmin in 1 tumor (2.3%). No tumor was positive for the S100 protein. All tumors that were KIT-negative were reevaluated for other immunohistochemical markers (like
vimentin) and with electron microscopy before they were classified as GISTs.

According to Fletcher’s criteria, 19 tumors (44.2%) were classified as high-risk, 7 (16.3%) as intermediate-risk, 12 (28%) as low-risk, and 5 (11.6%) as indeterminate-risk. We classified as indeterminate risk those patients whose original tumor was not identified and where only metastases were found. However, because they already had metastatic disease, they were added to the other 19 high-risk tumors giving rise to a total of 24 high-risk tumors (55.8%).

Eight GIST samples were observed on the electron microscope, including the 6 cases negative for CD 117. Among these cases, one revealed smooth muscle differentiation and the others had nonspecific features related to differentiation (CD117-positive cases were similar to CD117-negative cases).

In the 10 patients where the KIT mutation was studied, 5 had exon 11 mutations, 1 had an inconclusive exon 9 mutation, 1 had no definitely proven mutation in any exon, and 3 cases had no mutation. The cases where it was not possible to conclude anything with confidence were due to DNA low quality, and allowed no mutational analysis; the most probable cause of low quality DNA was related to the process of tumor tissue fixation.

The mortality rate caused by the tumor was 23.3% (10 deaths), all of them in high-risk patients. Only one death occurred in a patient with less than 5 years of disease duration. The mortality rate for the 9 patients with more than 5 years of disease duration was 42.9%. Metastatic disease was found in 13 patients (30.2%), 5 of them were deaths.

The 22 patients with less then 5 years since diagnosis have had not enough follow-up time to conclude anything, but 5 have already metastases and one is already dead.

**DISCUSSION**

Forty-three cases were diagnosed during a 10-year period. The incidence of GIST is 10 to 20 cases per million inhabitants per year, usually in patients above 50 years (4,6). In our case we found a mean incidence of 4.3 cases per 600,000 inhabitants.

The mean age of patients in the present series was similar to that recently published in the literature, with only a few cases below 50 years (6,8-12). However, the predominance of the male gender is not consensual (9,12,13).

From an epidemiologic point of view, sporadic cases of GIST are much more frequent, but some familial GIST syndromes are described. Familial GISTs are inherited in an autosomal dominant manner, with incomplete penetrance in the same genes as sporadic GISTs, alone or as a component of a syndrome associated with other tumors (like neurofibromatosis type 1) or GISTs associated with paragangliomas by allelic loss in the genes coding for succinate dehydrogenase subunits (Carney-Stratakis dyad) (13,14). No familial GIST was found in our series.

Gastrointestinal stromal tumors may arise anywhere in the gastrointestinal tract, and are more common in the stomach (60-70%), followed by the small bowel (20-25%), colon and rectum (5%), and esophagus (< 5%). Occasionally, they can also be found in extradigestive locations like the mesentery or the omentum (4,13). In the present series, as in others (9,10,13), we found only a small difference between gastric and small bowel tumors, and found no extradigestive GIST. However, other series found no differences at all (8) or even observed small bowel predominance (6) (Table III).

Clinical presentation is variable: GISTs can present as small, incidentally found nodules to large aggressive tumors (1,4) with nonspecific clinical symptoms (pain, discomfort, abdominal mass or digestive bleeding) (2). This variability is represented in the literature with a high percentage of asymptomatic incidental findings (6), as in our series, versus other published series with a majority of symptomatic patients (8,10-12).

Some literature reports gastric and rectal GISTs as smaller and less severe tumors in contrast to colonic or esophageal GISTs, which present as more aggressive neoplasias (1,4). Our results could not confirm these data as we found no tumors in the esophagus, colon or rectum, and we found some gastric high-risk lesions. Nevertheless, in 5 patients the tumor was never detected — only metastatic disease as in some other series (6,13).
Due to their stromal origin, GISTs typically grow as bulky, well-defined, endo- or exo-phytic masses parallel to the bowel lumen. Moreover, because of their variable clinical presentation there is no standard diagnostic protocol, so all imaging or endoscopic techniques may be used in the detection and location of these tumors. On endoscopic examination, GISTs are usually seen as submucosal lesions with normal or ulcerated mucosa (1), and on radiological examination as extrinsic digestive tract lesions (1).

Endoscopic ultrasonography (EUS) is the gold standard exam, although a definitive diagnosis is only possible with EUS-guided biopsy (2). Computed tomography (CT) is useful to evaluate tumor size, local extension, and staging.

Positron emission tomography (PET) is also a technique of choice for tumor staging, and is the best and most objective method to evaluate treatment response (with tyrosine kinase inhibitors) or when CT is inconclusive. If PET is not available, an alternative is CT with an adequate evaluation of tumor density (HU units).

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The main challenge is the differential diagnosis between GIST and other mesenchymal smooth-muscle tumors like leiomyoma, leiomyosarcoma, neurogenic tumors (schwannoma, neurofibrosarcoma) or other tumors (lipoma, liposarcoma, carcinoïd tumor, fibroma, desmoid tumor, and inflammatory fibroid polyp) (3,4).

Because their clinical behavior is highly variable, all GISTs are considered malignant tumors. Therefore, the older classification of “benign vs. malignant” tumor and the nonspecific denomination of “undetermined potential” were abandoned. New classifications were proposed that included risk assessment in predicting GIST behavior to metastatization (5).

According to Fletcher’s criteria, tumors with a low mitotic rate (≤ 5 mitoses per high-power field - HPF) or smaller size (< 2 cm) were generally less aggressive with a very low risk of metastasis. However, in the last decade, after a longer follow-up of GIST patients, it has been concluded that 50% of all resected GISTs will recur within 5 years, and more than 50% of high-risk tumors recur or metastize within 10 years. Furthermore, more and more descriptions have been published about tumors with a non-active mitotic rate that eventually metastasize (4,5). Our results corroborate data of low-risk patients having less severe disease. We also confirm the aggressive behavior of GISTs, with 50% of deaths occurring in non disseminated disease (5 in 10 patients), with 30.2% metastatic disease cases, 5 of them with no identification of the primitive tumor.

Tumor location and radiological features can also be used as prognostic factors but are not as accurate as the techniques described before (5). On CT, tumors with size > 5 cm, lobulated, with heterogeneity, that infiltrate adjacent adipose tissue, with regional lymph nodes or exophytic growing have a higher probability of progression to metastatic disease (5). Other authors report that rich vascularization may indicate a more aggressive tumor (8,16).

Table III. Comparative study

<table>
<thead>
<tr>
<th>Serie (study time)</th>
<th>No. patients</th>
<th>Mean age</th>
<th>Oesophagus</th>
<th>Stomach</th>
<th>Small bowel</th>
<th>Colon/rectum</th>
<th>Extraintestinal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Darnell et al. (14 years)</td>
<td>39</td>
<td>64</td>
<td>–</td>
<td>35.8</td>
<td>51.2</td>
<td>10.2</td>
<td>–</td>
</tr>
<tr>
<td>Salazar et al. (5 years)</td>
<td>17</td>
<td>64.5</td>
<td>–</td>
<td>29.4</td>
<td>64.6</td>
<td>–</td>
<td>5.8</td>
</tr>
<tr>
<td>Hidalgo et al. (6 years)</td>
<td>35</td>
<td>60</td>
<td>–</td>
<td>48</td>
<td>46</td>
<td>–</td>
<td>6</td>
</tr>
<tr>
<td>Rubio et al. (4 years)</td>
<td>46</td>
<td>63</td>
<td>–</td>
<td>50</td>
<td>43.5</td>
<td>2.2</td>
<td>4.3</td>
</tr>
<tr>
<td>Bertolini et al. (31 years)</td>
<td>118</td>
<td>66</td>
<td>–</td>
<td>57</td>
<td>31</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>Hassan et al.</td>
<td>191</td>
<td>65</td>
<td>–</td>
<td>54</td>
<td>36</td>
<td>10</td>
<td>–</td>
</tr>
<tr>
<td>Ahmed et al. (17 years)</td>
<td>185</td>
<td>64</td>
<td>9</td>
<td>52</td>
<td>16</td>
<td>17</td>
<td>6</td>
</tr>
<tr>
<td>Alvarado et al. (10 years)</td>
<td>275</td>
<td>61</td>
<td>2</td>
<td>40</td>
<td>35</td>
<td>12</td>
<td>10</td>
</tr>
<tr>
<td>Hinz et al. (12 years)</td>
<td>40</td>
<td>64</td>
<td>–</td>
<td>60</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>S. Alberto et al. (10 years)</td>
<td>43</td>
<td>62.7</td>
<td>–</td>
<td>46.5</td>
<td>41.9</td>
<td>11.6</td>
<td>–</td>
</tr>
</tbody>
</table>

List of published GIST series, comparing sizes series, patients’ mean age and tumor location.
After staging and excluding metastases by EUS, CT or PET, tumor resection is the standard therapy for localized GIST. Surgery includes complete resection of the tumor as en bloc removal (to make sure that its surrounding capsule remains intact) and assures negative margins (2, 17). As GISTs do rarely metastasize to lymph nodes, systematic lymph node dissection is unnecessary. In contrast, dissemination to the liver and peritoneum is common, and therefore a careful intra-abdominal exploration during surgery is recommended (2,8,17). Prognosis depends on tumor size and type of resection. Complete resection has a 5-year survival rate of 34% to 60% (7), which was also observed in our series.

Chemotherapy and radiotherapy are useless. Pharmacological treatment is based on non-selective tyrosine kinase inhibitors: imatinib and sunitinib. Imatinib is used as neoadjuvant therapy, in metastatic or residual disease after surgery, and there are also positive data on its use as adjuvant therapy. Sunitinib is a second-line therapy, after imatinib failure (only after having increased imatinib doses) or in case of imatinib intolerance (15).

Mutations involving exon 11 of c-Kit have a better prognosis and response to imatinib (17). Because we only studied the KIT mutation in more aggressive disease we cannot comment on these data.

CONCLUSIONS

A major difficulty with these malignant tumors is their diagnosis and subsequent prognosis, due to their rare and nonspecific symptoms. We highlight 42.9% of incidental findings.

Our results are in accordance with the literature worldwide, where a majority of cases are men, > 50 years of age, asymptomatic, and with a gastric tumor.

Most cases have a poor prognosis either according to Fletcher’s criteria or given the presence of metastasis.

We found KIT mutations in 50% of all 10 patients evaluated, with this value being lower than that in the literature.

Though our mortality rate (23.25%) was also lower than expected, 22 patients had recent disease (less than 5 years). In contrast, most deaths occurred in patients with disease duration > 5 years, which is closer to the reported 50% survival.

Fletcher’s criteria are a useful prognostic classification because when applicable they were consistent with the evolution and prognosis of disease.

We highlight the importance of submucosal lesions, most of them incidentally found, because most of them were GISTS; therefore, they are malignant and have a high risk of metastatization as well as high relapse and mortality rates.

REFERENCES