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ORIGINAL ARTICLE

# Gastrointestinal stromal tumor: pathological and clinical characteristics in the population of the General Hospital of Mexico "Dr. Eduardo Liceaga"

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## Abstract

*The gastrointestinal stromal tumors (GISTs) are neoplasms of mesenchymal origin; they represent 0.3% of neoplasm in the digestive tube. They are defined by the expression of CD117, a tyrosine kinase receptor of the growth factor. Our objective is to know the clinical, pathological, and immunohistochemical characteristics in the population who attend the general hospital of Mexico. The cases of mesenchymal tumors in the digestive system during the period of July 2010-May 2017 were revised. Fifty-four cases of GIST were found; in all cases, clinical data and the macroscopic aspect were studied, and microscopy and immunohistochemical characteristics were also checked. These cases are more frequent in women, in a proportion of 1.2:1, with an average age of 54-year-old. The treatment was full surgery, in 4 of them, a lymphadenectomy was done, and metastasis was found in one case. The average size of the tumors was 8 cm. The predominant histological pattern was fusocellular (81.5%), followed by epithelioid patterns (7.4%) and mixed (11.1%). The main locations were the stomach (48.1%), small intestine (40.7%), rectum (5.6%), omentum (3.7%), and mesentery (1.9%). The malignant potential according to Fletcher's criteria were very low malignant potential (20.5%), low malignant potential (25%), intermediate potential (20.5%), and high malignant potential (34.1%). All cases were positive for CD117.*

***Key words:*** *Gastrointestinal stromal tumor. C-KIT. CD117.*

## Introduction

These are neoplasms made up of spindle cells and/or epithelioid and occasionally pleomorphic cells, which originate from interstitial cells of Cajal (ICC), with mutations in the receptor tyrosine kinase genes, which distinguish them from other tumors.

In the decades from 30 to 50 of the 20th century, these tumors were classified as leiomyomas or leiomyosarcomas and tumors with epithelioid features were designated as leiomyoblastomas or epithelioid leiomyosarcomas.

Dudley cols in 1942 and Rabinovich et al. in 1949 considered that these neoplasms had a benign evolution. In counterpart France and Brenes in 1950, as well as Martin in 1960, they saw that some of these tumors were malignant and also suggest their myoid nature[1].

In the decade from 60 to 70, electron microscopy (EM) showed the absence of muscle differentiation.

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The term gastrointestinal stromal tumor (GIST) was introduced by Mazur and Clark[2] in 1983, working with immunohistochemistry (IHC) and ME techniques, determining that they did not have smooth muscle cell characteristics, whereas GIST was occasionally protein positive. S-100 proposes a Schwannian origin from the myenteric plexus.

In 1984, Herrera et al.[3] confirmed the neural nature of an intestinal malignancy by calling it plexosarcoma and because it coincided with a publication of a similar tumor with neuroendocrine differentiation by Walker and Dvorak these tumors were classified within the GIST, but considering a possible neuroendocrine differentiation[1].

In 1987, Barker and Rudolfe[4] succeeded in cloning the c-kit, using somatic human-mouse hybrid cells, locating the gene on chromosome 4. 2 years later, d'Auriol et al.[5] located the gene in the 4q11-q12 region.

In 1990, the mesenchymal nature of the tumor was confirmed by IHC, given that between 60% and 70% were positive for CD34 (hematopoiesis progenitor cell antigen), and this is being the first relatively specific marker of the GIST.

Kindblom et al.[6] argued that the GIST was related to the ICC, the myenteric plexus, and they form a network located in the plexus of Auerbach, regulating the communication between neurons and muscle fibers, and act as a pacemaker controlling peristalsis, muscle contraction, and possibly as mediators of neurotransmitters[7].

Histogenetically, ICC has a mesenchymal origin, and they differ from an intestinal precursor cell which also gives rise to smooth muscle cells. The expression of c-kit proto-oncogene and the precursor cell factor receptor would be necessary for the proliferation and differentiation of the precursor cells toward ICC[8].

The absence of neuroendocrine differentiation of ICC, evidenced by EM, excludes that these cells have a bifunctional, neural, and muscular capacity[9].

Kitamura et al.[10] discovered the increased function by mutation of the c-kit proto-oncogene and overexpression of CD117. Later, Lasota et al.[11] demonstrated that c-kit mutations and positivity for c-kit occurred only in GIST. In addition, the interaction between c-kit and its ligand factor precursor cells (stem cell factor) that binds to the intracellular receptor is vital for cell survival, proliferation, and differentiation.

Heinrich et al.[12] reported that the possibility of a second receptor involved in the pathogenesis of GIST was raised, especially in those lacking mutations in c-kit, and found a second in the platelet-dependent epidermal growth factor alpha (PDGFR$\alpha$) receptor.

In 2001, Joensuu et al.[13] described the first case of GIST, treated with imatinib, designed for the treatment of chronic myeloid leukemia, but which can act on proteins with tyrosine kinase activity, such as c-kit receptors and PDGFR$\alpha$ receptors.

The aim of this study was to describe the clinical pathological aspects and IHC of the neoplasms diagnosed as GIST, in the Surgical Pathology Unit from Hospital General de México "Dr. Eduardo Liceaga", during the period from July 2010 to May 2017, as well as review the literature relevant to this process.

## Materials and methods

We reviewed the cases of mesenchymal tumors of the digestive system, during the period from July 2010 to May 2017, which had lamellae and paraffin blocks, to make additional histological sections if necessary; likewise, they had studies of IHC, for CD117, anti-smooth muscle actin (AAML), and S-100 protein (PS-100).

From the microscopic study and IHC of the mesenchymal tumors, 54 were found which fulfilled the GIST criteria. The microscopic study also allowed obtaining data regarding histological pattern, number of mitosis, histological type, state of the borders, necrosis, and differentiation. From the anatomopathological report, data were obtained on the clinical diagnosis, age and sex of the patient, and size and location of the tumor, and with all this information, an overview of the risk factors was formed, which determine the malignant behavior of these neoplasms.

## Results

In 54 cases of GIST, the clinical diagnosis was of tumor in 28 cases (51.9%), of probable GIST in 21 (38.9 %), gastric Ca in 3 cases (5.6%), perforation of 1 case (1.9%), and acute abdomen in 1 case (1.9%). The average age of the group was 54 years, with limits between 22 years the least and 81 years the highest. Regarding sex, 29 cases (53.7%) were women and 25 (46.7%) were men. The ratio of women to men is 1.2:1.

Regarding localization, 26 cases (48.1%) were in the stomach, 5 (9.3%) in the duodenum, 8 (14.8%) in the jejunum, 9 cases (16.7%) in the ileum, 3 (5.6%) in the rectum, 2 (3.7%) in omentum, and 1 (1.9) in the mesentery. When correlating the location with the age group, it was found that, in 24 cases (44.4%), it was between 21 and 50-year-old, 25 cases (46.3.3%) between 51 and 75-year-old, and 5 (9.3 %%) >75-year-old

**Table 1.** Age and location

| Age groups | Locations | | | | | | |
|---|---|---|---|---|---|---|---|
| | Stomach | Duodenum | Jejunum | Ilium | Rectum | Epiplon | Mesentery |
| <20 years | | | | | | | |
| 21-50 years | 10 | 4 | 4 | 5 | 1 | | |
| 51-75 years | 13 | 1 | 4 | 3 | 1 | 2 | |
| >75 years | 3 | | | 1 | 1 | | 1 |
| Total | 26 | 5 | 8 | 9 | 3 | 2 | 1 |

**Table 2.** Size and staging of neoplasias in 44*

| Cases | | | | |
|---|---|---|---|---|
| Location | < 2 cm | 2 cm < 5 cm | > 5 cm < 10 cm | > 10 cm |
| | T1 | T2 | T3 | T4 |
| Stomach | | 5 | 7 | 7 |
| Duodenun | | 5 | | |
| Yeyunum | 1 | | 1 | 1 |
| Ilium | 1 | 2 | 3 | 4 |
| Rectum | 1 | | 1 | |
| Epiplón | | 2 | 2 | |
| Mesentery | | | | 1 |
| Total | 3 (6.8%) | 14 (31.8%) | 14 (31.8%) | 13 (29.6%) |

*Ten cases were biopsies or cases of revision of lamellae, therefore there is no data on the size of the tumor.

**Table 3.** Index of mythosis for 50 fields of great increase

| Location | < 2 to 2 | 2 to < 5 | > 5 to < 10 | > 10 |
|---|---|---|---|---|
| Stomach | 18 | 3 | 2 | 3 |
| Duodenun | 5 | | | |
| Yeyunum | 5 | 1 | 1 | 1 |
| Ilium | 3 | 3 | 2 | 1 |
| Rectum | 1 | 1 | 1 | |
| Epiplón | | 1 | | 1 |
| Mesentery | | | | 1 |
| Total | 32 (59.3%) | 9 (16.7%) | 6 (11.1%) | 7 (12.9%) |

(Table 1). The size of the tumors could only be obtained in 44 of the 54 cases and ranged from 1 cm the least to 30 cm the greatest, with an average of 8 cm. (Fig. 1); nevertheless, tumors of 1 cm only there were 1 (2.3%) and tumors > 10 cm. 13 (29.6%) (Table 2).

Regarding the mitosis index for 50 high-gain fields (CGA, by its abbreviation in Spanish), we found < 2.32 cases (59.3%); > 2 < 5 mitosis for 50 CGA, 9 (16.7%); > 5 < 10 mitosis for 50 CGA, 6 (11.1%); and > 10 mitosis for 50 CGA, 7 (12.9%) (Table 3).

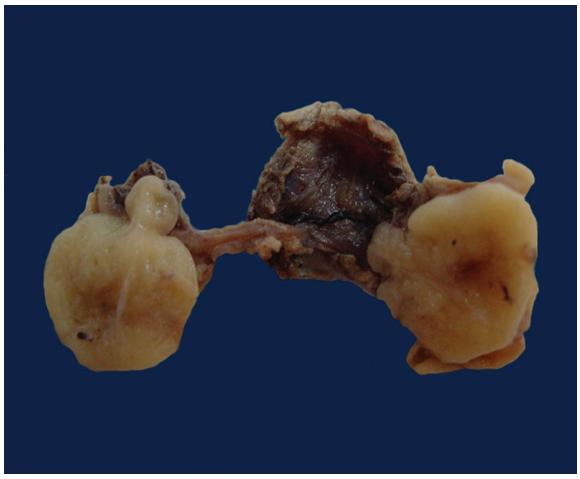

**Figure 1.** Macrophotography of duodenal gastrointestinal stromal tumor, well limited, rounded, grayish brown and fasciculate appearance.

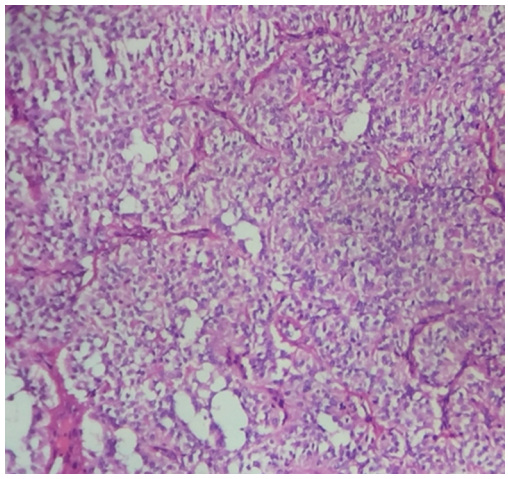

**Figure 3.** Gastrointestinal stromal tumor of epithelioid type with a pseudoalveolar histological pattern HE ×200.

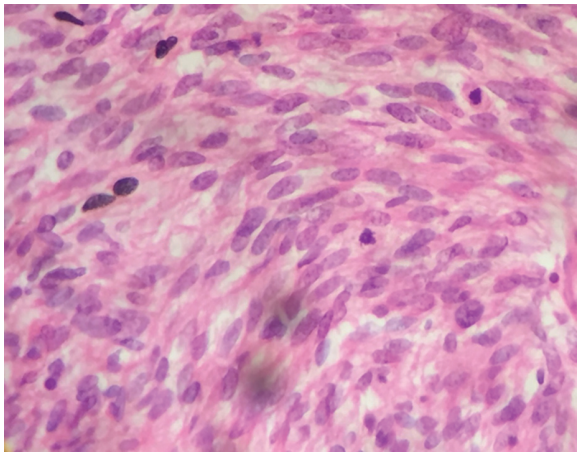

**Figure 2.** Microscopic image of gastrointestinal stromal tumor with a fusocellular pattern and a mitosis figure in the central part of the HE ×200 image.

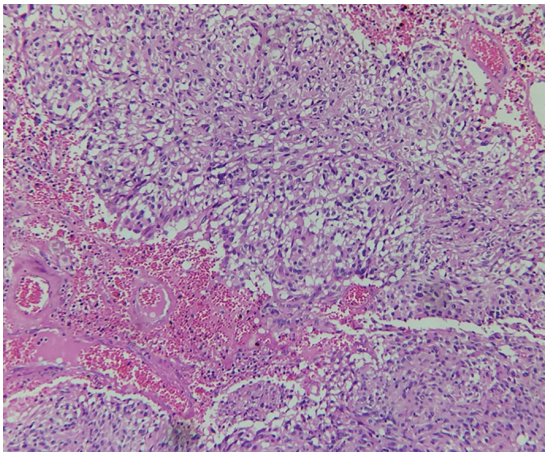

**Figure 4.** Microphotography showing a mixed image of gastrointestinal stromal tumor, a fusocellular pattern and an epithelioid HE ×400.

Regarding the histological type, the fusiform variety (Fig. 2) was present in 44 cases (81.5%), the epithelioid form (Fig. 3) in 4 cases (7.4%), and mixed type (Fig. 4) in 6 cases (11.1%). Regarding the borders, 41 cases (78.8%) had rounded edges and 11 (21.2%) had infiltrating edges. In the cases with infiltrating edges, 6 tumors were gastric, 2 of jejunum, 2 of ileum, and 1 of mesentery. Two more cases corresponded to biopsies, and it was not possible to determine the characteristics of the infiltration.

In the IHC study of the 54 cases, all were positive for CD117 (Fig. 5) and the reactions for AAML and PS-100 were negative. In four cases, lymphadenectomy was performed, and in one case of high-grade jejunum GIST, there was metastasis to a regional lymph node (Fig. 6).

## Discussion

GIST is neoplasms of mesenchymal origin, constituting a group of lesions characterized immunohistochemically by expressing in >90% of cases the transmembrane receptor derived from the stem cell, with activity on the receptor tyrosine kinase known as CD117 or c-kit.

The incidence of GIST is 10-20 cases per 10,00,000 inhabitants. It occurs around 50 years with an average

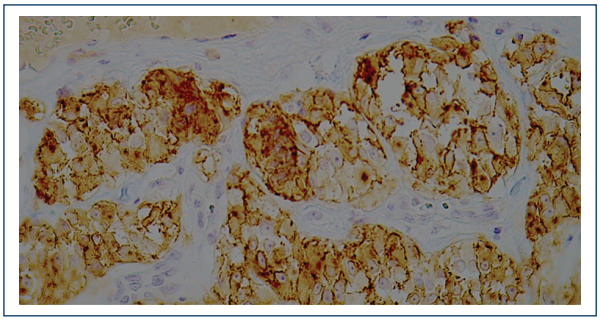

**Figure 5.** Positive immunohistochemistry for CD117 in an epithelioid-type gastrointestinal stromal tumor.

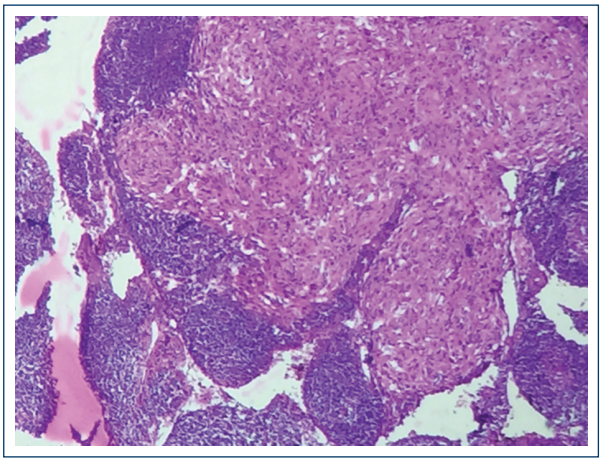

**Figure 6.** Ganglionar metastasis.

of 55-65 years. In our cases, the youngest was 22-year-old and the oldest 81-year-old, with an average of 54 years, which agrees with that reported in the literature. It is most commonly located in the stomach (50%-60%), followed by the small intestine (20%), colon and rectum (10%), and esophagus (<5%). Occasionally, they are located in omentum, mesentery, retroperitoneum, pancreas, and gallbladder[14]. In our tumors, it was in descending order: the stomach (48.1%), small intestine (40.8%), rectum (5.6%), omentum (3.7%), and mesentery (1.9%).

The symptoms depend on the size of the GIST; thus, gastric tumors present with abdominal pain or hemorrhage. In GIST of the small intestine are pain, hemorrhage or signs of obstruction[15]. In the Mexican population, Medina et al.[16] found that the main symptoms are abdominal pain (56%), digestive tract hemorrhage (38.7%) anemia (34.1%), vomiting (16.1%), abdominal distension (12.9%), weight loss (12.9%), and postprandial fullness (6.5%).

The reported size of the tumors is between 0.3 cm the smallest and 38 cm the oldest. We found that the largest tumor was 30 cm and the smaller than 1 cm with an average of 8 cm. As for gender, they occur more frequently in men; however, in our casuistry, the woman was mostly affected in a 1.2:1 ratio.

Within the organ affected by the tumor, it may have an intramural, submucosal, or suberosa location. When cut the surface is of variable color depending on the degree of hemorrhage, its color may be grayish, whitish, reddish, or brownish. They are usually fleshy looking solids, with cystic or necrotic areas[17]. Of our cases, 13 had necrosis, 10 of which measured >10 cm and 3 <10 cm.

Histologically, GIST presents different cell morphologies: spindle cells (77%), epithelioid cells (8%), and the mixed form (15%)[14]. The proportion found in our casuistry was spindle cells (81.5%), cell epithelioid (7.4%), and mixed variety (11.1%).

Fusocellular tumors are composed of cells with a fusiform nucleus, scarce eosinophilic or pale cytoplasm, and a fibrillar aspect. They grow without a defined pattern, fusocellular, verticillate, storiform, or palisading, like peripheral nerve tumors. In the cases of this report, we found two with neurofibroma-like pattern, one with a storiform pattern, and the other with cellular pleomorphism.

Epithelioid tumors have extensive, eosinophilic, oncocytic, or clear cytoplasm; they can present perinuclear glycogen, and the histological pattern can be organoid, trabecular, alveolar, or insular. Mixed tumors show transition between the epithelioid and spindle cell fields.

Between 80% and 100% of GISTs show mutations in one or both tyrosine kinase receptors, which are the kit gene and PDGFR$\alpha$. Tyrosine kinase is detectable by IHC with CD117 antigen, which produces a strong and diffuse staining cytoplasmic. Our cases were all positive (54/54) to CD117.

A small proportion of GIST is negative for CD117; in this situation, a marker that is independent of the kit or PDGFRa mutations has been described, and it is a protein of the calcium and chlorine regulatory channel called DOG 1 (Anoctamin 1). It is an antibody with greater sensitivity to CD117 but with relative specificity, since it has been positive in several carcinomas and some sarcomas[18,19]. Negative cases of DOG and kit can be diagnosed with the protein kinase theta, which is expressed in all GISTs regardless of their mutational status[20].

The mutation of the kit gene is an early event in GIST, with the mutation of exon 11 being the most common.

Secondary mutations are also found in exons 13, 14, 17, or 18. Studies of mutations are necessary when GISTs do not react to CD117[19,21].

Approximately 10% of GISTs do not detect mutations in c-kit or PDGFRa and it is called wild-type (WT); in spite of not detecting these mutations, the tyrosine kinase is activated. In the GIST of the WT variety, several oncogenic mutations have been described, such as BRAF, which encodes a serine/threonine protein kinase, which plays an important role in the regulation of the cell cycle and oncogenic modification of cellular responses to growth signals via Mitogen-activated protein kinase[22].

Between 2005 and 2006, Miettinen and Lasota[23] added the location parameter to the Fletcher[24] classification, finding that the intestinal GIST of the jejunum and ileum with a similar size and mitosis activity to the gastric ones are more aggressive. In our cases, there are few examples and we do not have data on the evolution after surgery, of the GIST reported here, to reach these conclusions (Tables 2 and 3). However, in Mexico, Medrano et al.[25] found, in a study of 66 cases of GIST, that the variable that showed statistical significance in survival was localization, and in intestinal lesions, the survival was lower.

In 2010, the International Union Against Cancer (UICC)[26] presented a new classification TNM: T1 tumor <2 cm, T2 tumor >2 cm >5 cm, T3 tumor >5 cm <10 cm, and T4 tumor >10 cm. According to this classification, our cases behaved as follows: T1, 3 cases (6.8%); T2, 14 cases (31.8%); T3, 14 cases (31.8%); and T4, 13 cases (29.6%) (Table 2).

The same UICC ensures the histological grade according to the number of mitoses by 50 CGA: low grade, when the mitosis count is <5 per 50 CGA, and high grade, when the count is >5mitosis per 50 CGA. Regarding the histological grade, our cases presented the following behavior: low grade 41 cases (75.9%) and high grade 13 cases (24.1%) (Table 3).

The prognostic factors to be considered in the GIST are several and include localization, and tumors that originate in the small intestine and rectum have a worse prognosis[24]. Peritoneal or hepatic metastases are of worse prognosis.

Small tumors, incidental in the serosa, have a favorable course[27]. Other factors are tumor size, number of mitoses per 50 CGA, spontaneous or iatrogenic rupture of the tumor, affected surgical margins, necrosis, nuclear atypia, muscle, or mucosal invasion[28]. Ki 67 >10% is associated with poor prognosis[31]. In the Mexican population, Martínez et al.[29] found that the expression of p53 is greater in lesions of the intestine than in the stomach. Ki 67 >10% is associated with poor prognosis[30].

The treatment of choice is complete surgical resection; lymphadenectomy is not necessary since lymphatic dissemination is unlikely[31]. Lymphadenectomy was performed in 4 of our cases, and one of them identified metastases in 1 lymph node.

GIST is resistant to radio- and chemo-therapy and has recurrence or metastasis in 20%-50% of patients with resectable tumors; nevertheless, imatinib, in the postoperative period, has managed to improve recurrence-free survival. With imatinib, the best results are given when there is a mutation of exon 11 and greater resistance with mutations of exon 9 and the PDGFRa gene. When there is resistance, second-generation chemotherapy drugs such as sunitinib or regorafenib can be used[32].

The application of micro-RNA (myRNA) in the treatment of GIST is under the study, and they are agents that can provoke an immune response[17]. The miRNA, which is small single-stranded RNA encoding 19-22 nucleotides, has the ability to regulate gene expression by translational inhibition or degradation of messenger RNA[33].

Early diagnosis and radical resection of the primary lesion are the most appropriate treatment for healing.

In our cases, the main treatment used was surgical resection, and we do not have data on the subsequent evolution of patients.

## Ethical disclosures

**Protection of human and animal subjects.** The authors declare that no experiments were performed on humans or animals for this study.

**Confidentiality of data.** The authors declare that they have followed the protocols of their work center on the publication of patient data.

**Right to privacy and informed consent**. The authors declare that no patient data appear in this article.

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