Gastrointestinal Stromal Tumors (GISTs)

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Review Article

General Surgery

OPEN ACCESS

Background:
Gastrointestinal stromal tumors are a specific kind of mesenchymal tumors, predominant benign with different histological patrons, epidemiology in Mexico suggest gastric GIST, as the most common, the clinical manifestations and the imaging characteristics are essentials fot the diagnostic suspicion, among the most commonly used studies are computed tomography, magnetic resonance, ultrasound and positron emission tomography with fluorodeoxyglucose. Management is multidisciplinary and depends on the histological characteristics as well as the response to chemotherapy Gastrointestinal stromal tumors are a specific kind of mesenchymal tumors, predominant benign with different histological patrons, epidemiology in Mexico suggest gastric GIST, as the most common, the clinical manifestations and the imaging characteristics are essentials for the diagnostic suspicion, among the most commonly used studies are computed tomography, magnetic resonance, ultrasound and positron emission tomography with fluorodeoxyglucose. Management is multidisciplinary and depends on the histological characteristics as well as the response to chemotherapy.

KEYWORDS:
GIST, Gastro intestinal stromal tumor

Cancer is a widespread pathology worldwide, being in some areas the first and second cause of death before the age of 70 and in other countries the third and fourth cause. It is known that it generates a total of 9,958,133 deaths worldwide, whereas, in Central America, Mexico leads this mortality with a total of 90, 222 (71.6%) of the deaths [1].

According to Globocan in 2020, stomach cancer is the fifth most common cancer worldwide, corresponding to an incidence of 5.6% of all cancers (1,089,103) [2].

In Mexico, it is the sixth most common cancer, with an incidence of 4.5% of all cancers (8,804) [3].

Within the classification of gastrointestinal tumors, stromal tumors are the most frequent of the mesenchymal tumors of the gastrointestinal tract, constituting approximately 80% of all these gastrointestinal tumors and 0.1 to 3% of gastrointestinal malignancies. Approximately 30% of all GIST are malignant, the most frequent being gastric (60%) and small intestine (20-30%), but rarely they can also be found in the omentum, mesentery, and retroperitoneum. Previously they were described as originating from smooth muscle, but for the last 20 years, thanks to immunohistochemistry, they have been recognized as a separate entity known as GIST [4].

Advances in the study of pathology, immunohistochemistry, and molecular biology in recent years have improved the ability to diagnose GIST. Its origin is now considered to be Cajal interstitial cells expressing CD-117 (a product of the c-KIT proto-oncogene) and harboring a c-kit or platelet-derived growth factor receptor alpha (PDGFRA)-dependent mutation [5].

Epidemiology

It is known that in Mexico there is little literature about the epidemiology of gastrointestinal tumors. One of these, reported by the Mexican Association of General Surgery presents 44 cases and is known as the GIST Project (Mexico, 2005-2007). This was a national multicenter, multidisciplinary and interinstitutional project involving 37 researchers who found an incidence of 54.5% of cases in women. From 8-87 years of age, with a mean age of 57 years. 40.9% of these tumors were in the stomach. The average tumor size was 11.6 cm and only 46% were confined to the affected organ [6].

In another more recent study also carried out in Mexico, 114 gastrointestinal tumors were documented from February 1, 2014, to March 31, 2020, of which 50 were of epithelial origin. The most frequent was gastric adenocarcinoma with 34 cases in total, followed by duodenal adenocarcinoma with 6

From the General Surgery Departament at Regional General Hospital No. 66, Ciudad Juárez, México. Received on January 19, 2025. Accepted on January 24, 2025. Published on January 26, 2025.

DOI 10.5281/zenodo.14744305

cases, 36 were mesenchymal (28.93%) of which 16 (14.03%) corresponded to GIST. Of these, 7 (43.75%) were gastric GISTs and 9 were intestinal GISTs (56.25%); 4 were located in the duodenum (25%), 3 in the jejunum (18.8%), and 2 in the ileum (12.5%). The age of the cohort was 55 years and only 12.5% had a family history of neoplasia (1 case with a father with unspecified gastric cancer and a brother with pancreatic cancer) and a second patient with relatives with unspecified cancer [7].

GIST has a higher incidence in patients between 50-80 years of age, with no gender predominance. However, there are GISTs observed in younger patients, mainly with genetic predisposition such as neurofibromatosis type 1, Carney's triad, Carney-Stratakis syndrome, or KIT germline mutations [8].

In recent years, advances have been directed towards well-defined areas: molecular tumor biology and development of new drugs; consolidation of the technical principles of GIST surgery and the role of laparoscopy; management of GIST in uncommon locations and advanced GIST [9].

Clinical presentation

In the clinical presentation of GIST, the patient is asymptomatic in 18% of cases, especially in cases of small tumors of the gastrointestinal tract. These are usually findings in CT scans, endoscopy, or during surgical procedures for other manifestations. Symptomatic patients may present nonspecific symptoms such as nausea, vomiting, abdominal distension, early satiety, abdominal pain, and rarely palpable tumor. Large tumors can generate gastrointestinal obstruction in the lumen by endophytic growth or compression of the gastrointestinal tract that can lead to dysphagia, obstructive jaundice, and/or constipation depending on the location of the tumor. A perforated tumor may be found with signs and symptoms of peritonitis or gastrointestinal bleeding. An indolent intraperitoneal bleeding tumor is secondary to necrosis and ulceration [10].

Bleeding, pain, and weight loss are frequent symptoms. The presence of a clinically noticeable abdominal mass is not unusual, as some GISTs may grow slowly with limited symptoms over a long period. Some patients with GISTs present as emergencies due to, for example, upper gastrointestinal bleeding, intestinal occlusion, or, particularly in small bowel GISTs, perforation. In these patients, emergency surgery may not follow standard oncologic guidelines, affecting the patient's long-term prognosis [11].

Pathogenesis

Originally, histopathologic observation led one to believe that GISTs originate from smooth muscle. They do not, however, have the same immunohistochemical profile as leiomyomas and leiomyosarcomas that originate from other locations, such as the uterus or soft tissues. More than 95% of GIST cases have a predominant expression of the CD117 antigen, while leiomyosarcomas, leiomyomas, and other gastrointestinal tract spindle cell tumors are typically CD117-negative. The transmembrane KIT receptor tyrosine kinase, or c-KIT—the human homolog of the viral oncogene v-KIT—is the product of the KIT proto-oncogene and is represented by the CD117 antigen. [12].

Approximately 80% of GISTs carry a mutation in the KIT gene, resulting in a structural variant of the KIT protein that is abnormally activated and enables oncogenic signaling in the cell. GISTs likely originate in the interstitial cells of Cajal (ICCs), sometimes referred to as gastrointestinal pacemaker cells, which are located in the intramuscular layer of the intestinal wall beneath the epithelium; they regulate peristalsis by forming the interface between the autonomic innervation of the intestinal wall and the smooth muscle itself. GISTs arising in the GI tract typically present as subepithelial masses, which is generally consistent with the primary location of ICCs. ICCs have the immunophenotypic and ultrastructural features of smooth muscle and neuronal differentiation. GISTs are speculated to originate from CD34-positive ICC stem cells within the wall of the GI tract and differentiate toward the pacemaker cell phenotype. Therefore, a link between GISTs and ICCs has been proposed because both cell types can express KIT protein and CD34.12 An exception is the extremely rare “extragastrointestinal stromal tumor” (EGIST), a primary GIST that arises outside the GI tract. EGISTs are phenotypically identical to true GIST lesions of the GI tract. Although this finding appears to contradict the hypothesis that GISTs arise from ICCs within the intestinal wall, these tumors are thought to arise from ICCs that were accidentally dispersed during embryogenesis [13].

Supporting the origin of GISTs from ICCs, some tumors have presented diffuse ICC hyperplasia in the wall of the proximal gastrointestinal tract in several families with primary familial GIST. These are thought to represent precursor lesions to GIST in these patients. In these cases, they must be distinguished from syndromic ICC hyperplasia seen in inherited syndromes characterized by the development of GIST [12].

DOI 10.5281/zenodo.14744305

Several studies have elucidated the genetic events responsible for the transformation of microscopic GIST lesions, for example, homozygous inactivation of the basic helix-loop-helix leucine zipper-type transcription factor (bHLHZ) and the MYC-associated factor X (MAX) transcription factor led to p16 inactivation and cell cycle perturbation. The presence of MAX inactivation in both microscopic/low-risk GIST and metastatic GIST from the same patient indicates that it is likely an early step in GIST progression. Furthermore, dystrophin inactivation (DMD, chromosome Xp21.1), which was present in more than 90% of metastatic GIST in one study, is likely a late event in GIST progression [13].

Etiology

Etiological classification of GIST

The majority of GIST cases are sporadic, while roughly 5% are associated with a family of hereditary disorders that includes: Carney-Stratakis syndrome, Carney triad syndrome, Familial neurofibromatosis type 1 (NF1), and primary familial GIST syndrome. From a phenotypic, histological, or molecular perspective, sporadic occurrences of GIST are now indistinguishable from familial cases of GIST. An average diagnosis of Carney-Stratakis syndrome is made between the ages of 19 and 21. Typically, these individuals have paragangliomas in addition to GIST. Young women with paragangliomas, pulmonary chondromas, and GIST are diagnosed with the Carney triad. It has been demonstrated that the succinate dehydrogenase (SDH) subunit genes are mutated and undergo methylation alterations in Carney-Stratakis syndrome and Carney triad, which ultimately result in a universal SDH deficit. On the other hand, patients with primary familial GIST and NF1 continue to be SDH-proficient. In SDH deficient syndromes, treatment and follow-up recommendations are different. In most cases, these patients are part of clinical trials, or their treatment is carried out in tertiary care centers. Data suggests that surgical resection may not be beneficial for some patients with tumors without a KIT/PDGFRA mutation. In addition, SDH-deficient GISTs are often resistant to tyrosine kinase inhibitors (TKIs), which are typically used in patients with advanced GISTs and a KIT/PDGFRA mutation. This may be explained by the absence of gain-of-function tyrosine kinase mutation. Nevertheless, some individuals with SDH-deficient GIST may benefit from this treatment, despite the limited effectiveness of these therapeutic drugs having been shown. Regarding the surveillance of patients with SDH-deficient GIST, there are no generally accepted recommendations. In addition, asymptomatic individuals carrying the SDHx mutation should be monitored, due to their predisposition to develop neoplastic disorders [12].

The small bowel accounts for over 70% of GIST cases associated with NF1 syndrome. They are frequently multifocal tumors with low mitotic rates. Unlike sporadic GISTs, mutations in the PDGFRA and KIT genes are rare in these cases. The hallmark of primary familial GIST syndrome is a propensity for many early-stage stomach or small intestine tumors to grow. Individuals who have germline mutations in the PDGFRA genes are related to inflammatory fibroid polyps or intestinal fibromatosis, while patients with mutations in the KIT genes may be associated with paragangliomas, dysphagia, or skin hyperpigmentation. The tumor manifests at the subepithelial level, contingent upon the origin of the cells [11].

Histological classification of GISTs

Macroscopically, GISTs are white, well-defined, non-encapsulated, and firm in consistency. The surface of the section may be homogeneous, seen mainly in small GISTs, or heterogeneous, with areas of hemorrhage and necrosis in larger tumors. In small tumors, the covering mucosa remains unchanged (apparently normal), but in larger and more aggressive tumors, it may ulcerate. Microscopically, GISTs can be divided into three main types: Spindle cell type, Epithelioid type and Mixed type. Spindle cell type GISTs are composed of eosinophilic cells that have a slightly paler cytoplasm compared to that of leiomyoma [12].

Epithelial GISTs are composed of rounded epithelioid cells that have clear eosinophilic cytoplasm and round or oval nuclei. Tumors of this type are mostly located in the stomach and are most often negative for KIT expression [14].

Mixed-type GISTs are tumors that contain both spindle cell and epithelioid cell types [13].

Immunohistochemical classification of GISTs

Markers that may contribute to the differentiation of GISTs from other tumors of the gastrointestinal tract are GAME (CD117), DOG-1 (discovered in GIST-1), protein kinase C theta (PKC-theta), and other markers like CD34 and smooth muscle actin.

Molecular classification of GIST

From a molecular point of view, the mutations found are the following: almost 75% of cases harbor KIT mutations (commonly in exons 11, 9 and in rare cases in exons 13, 17, 14, and 18). A total of 10% of cases harbor PDGFRA mutations (exon 18: D842V

DOI 10.5281/zenodo.14744305

with significant imatinib resistance and non-D842V with imatinib sensitivity; exon 12 and, rarely, exons 14 and 10) [14].

In total, 10-15% are KIT/PDGFRA wild-type: one-third (20-40%) have SDH deficiency: SDHx mutations or SDHC promoter hypermethylation. NF1 or BRAF genetic mutations are present in approximately 13% of cases. Rarer events include ETV6-NTRK3 fusions, FGFR1 fusion or point mutations, and FGF4 duplication [15].

KIT/PDGFRA wild-type (WT GIST) GISTs correspond to those that do not have mutations in KIT/PDGFRA. Currently, detailed molecular analysis has shown that this group is heterogeneous and has several mutations [16].

Imaging

Computed axial tomography

Contrast-enhanced computed axial tomography is the first-line modality for the diagnosis of GIST. It typically presents as a lobulated but well-circumscribed image, with heterogeneous enhancement centered on the intestinal wall. It tends to be large, with an approximate size of 3-10 cm at the time of diagnosis. The variation in size usually reflects the indolent nature of growth and the lack of associated symptoms in this type of lesion. Small bowel distension has increased sensitivity for lesions in the intestinal lumen. A CT enterography has greater sensitivity for the diagnosis of GIST than a simple, contrast-enhanced CT of the abdomen and pelvis. Sometimes they are small tumors, which can be located in the stomach and duodenum, with enhancement in the arterial phase. Attenuation is greater in patients with duodenal tumors. Vascularity can be seen better in the portal phase. Vascularity is related to the aggressive nature of the tumor. In large lesions, internal bleeding, cyst formation, necrosis, ulceration, and a combination of both may occur. Hemorrhage may be distinguishable as high intrinsic attenuation on nonenlarged, non-contrast images or postcontrast images. Cyst formation, especially in lesions along the lesser curvature of the stomach or duodenum, often mimics a mucinous cyst or pancreatic cysts such as pancreatic mucinous neoplasms or pseudocysts. Occasionally, necrosis may generate cavitation and gas collection with the lesion; this is rare but is important in the diagnosis. The Torricelli-Bernoulli sign, seen as increasing necrosis, should be considered, describing an ulcerated gastric leiomyosarcoma and confirming a gastrointestinal tumor. Calcifications may be seen on atypical images. The exophytic component almost always predominates over the endophytic component, concentric lesions are generally more associated with adenocarcinoma [17].

Magnetic resonance imaging

The characteristics of both (GIST and E-GIST) are similar to those of CT. It has been reported that with the use of MRI it is more difficult to differentiate an incidental GIST compared to CT, generally due to gas and peristalsis artifacts. It is more sensitive to metastatic liver lesions than CT and can be useful for staging. It is also better at evaluating anorectal GIST than CT [17].

Ultrasound

It has not been used historically, but some techniques allow intestinal pathology to be appreciated in transabdominal ultrasound. It can be seen as isoechoic and hypoechoic, in the intestinal wall. The characteristics that will be described are dependent on the size of the lesion and whether there is necrosis or hemorrhage. Contrast ultrasound can help or suggest an abdominal GIST, generally hypervascular with a slow arterial washout phase and a delayed venous washout phase. It can help if differentiation is required for a directed biopsy [17].

FDG-PET/CT Positron Emission Tomography with Fluorodeoxyglucose

It has a role in staging, both in the evaluation of solid organ metastasis and nodal metastasis compared to CT alone. In intestinal lesions, it may be limited for the visualization of intrinsic lesions, in addition to intestinal physiological activity, hypermetabolic GIST can sometimes be seen [17].

Another diagnostic method is biopsy, some literature is skeptical of this diagnostic method, but a study was conducted based on 3 randomized studies and 7 hospitals, where 350 patients were considered who could be eligible for inclusion and one case of GIST in the biopsy tract with a coaxial needle sheath. It is concluded that there is no relevant risk (0.37%) for needle tract implantation or abdominal recurrence after pre-biopsy treatment for GIST (Imatinib) and it may be safe with the correct technique to differentiate GIST from other resections [18].

The use of endoscopic ultrasound provides a better sample for biopsy compared to the normal forceps technique in endoscopy of 85-94% in biopsy with endoscopic ultrasound vs. 17-59% with the conventional method [19].

DOI 10.5281/zenodo.14744305

Treatment

Surgical treatment

The cornerstone of treatment is complete resection of localized GIST, tumors up to 2 cm are considered easy to resect; laparoscopic surgical resection is the treatment of choice [20,21].

The objective of surgery is to obtain a complete abdominal exploration, complete resection (R0), with negative margins and without rupture of the tumor pseudocapsule, avoid lymphadenectomy, observe the entire cavity, unnecessary wide margins (1 cm), and if there is a positive margin (R1) consider re-resection. Resection of tumors smaller than 5 cm can be carried out laparoscopically and is safe and effective [22].

The considerations to take into account, in addition to those previously described for laparoscopic surgery, are to avoid its use if it is not possible to obtain R0, not to use it in tumors larger than 10 cm, and it can be used in tumors smaller than 5 cm with favorable anatomical location, location in the greater curvature, fundus and anterior gastric surface. Tumors in the gastroesophageal junction, cardia, lesser curvature, posterior surface, or antrum/pylorus present difficulty with laparoscopy and benefit from open management. Surgical removal should always be performed in a bag to avoid implantation in the abdominal wall [23].

The gold standard in the treatment of GISTs is surgical management with preferably laparoscopic resection, however in unstable patients or those with large tumors, laparotomy is preferred as a treatment method [24].

A prospective study in Romania from May 2012 to May 2017 was analyzed, where 48 patients underwent surgery, and of these, 25 had gastric tumors (52.08%). 9 laparoscopic and 16 open resections were performed on tumors larger than 10 cm. In the histopathological tests, 10 patients (40%) were risk class 3a / 3b. Complications were more frequent in open surgery with a range of 43% (7 patients) vs 33.3% (3 patients). It is concluded that in experienced centers laparoscopic surgery can be performed safely in tumors > 5 cm [25].

Another laparoscopic study was evaluated, which demonstrated a decrease in bleeding, lower risk of complications in laparoscopic surgery, and shorter hospital stay compared to open resection. [26].

In addition to what was previously mentioned: size, mitotic index, location, and rupture are the 4 most important factors for prognosis. The size limit is 5 cm, in those smaller than 5 cm the prognosis is better. As GIST typically has a low mitotic index, 50 high-power fields, greater than the typical 10, is used as a margin for mitotic activity. Other factors include the use of imatinib and recurrence after curative resection [27].

In patients with localized disease but at high risk of recurrence, imatinib may be given for a minimum of 3 years. For this, the Miettinen classification, also known as the Armed Forces Institute of Pathology classification, is used, which evaluates the mitotic index, tumor size, and location [28].

A study was conducted by Chul Honh Park, et al. at Busan National University Hospital (Busan, Korea) between February 2001 and June 2012 with 145 patients who underwent surgery. Two staging systems were evaluated, the UICC/AJCC TNM staging system and the NIH consensus criteria, suggesting that the former may be a better option. It is concluded that the UICC/AJCC TNM staging system may be more useful than the NIH consensus criteria for risk categorization of patients with gastric GIST [29].

Medical treatment

Among the well-established medical treatments available are tyrosine kinase inhibitors, among which is imatinib, which is a 2-phenylamino pyrimidine derivative and inhibits the BCR-ABL protein, ABL, KIT and PGFRs (growth factor receptors). It is water-soluble and absorbed in the gastrointestinal tract, binds to albumin, and in part to a1-acid glycoprotein in the blood, and is metabolized in the liver by CYP3A4. With a median disease-free survival of about 2 years. Biomarkers for activity include blood levels of the drug, GIST genotype, initial tumor volume, patient status, white blood cell count, and serum albumin. Sunitinib is an oxindole derivative, it is a multitarget receptor tyrosine kinase inhibitor, specifically KIT, VEGFR 1-2-3, PDGFRA, PDGFRB, KIT, RET, and FLT3 inhibitors. It has lower bioavailability than imatinib, and their metabolic pathways are similar. It is used as the second line in imatinib-resistant GIST, the median survival after starting sunitinib and imatinib is about 1.5 to 5 years respectively. Regorafenib is a diphenylurea, it has multitarget tyrosine kinase inhibitors and KIT, VEGFRs, PDGFRs, TIE 2, FGFR, RET, RAF-1, and BRAF inhibitors. It has gastrointestinal absorption and protein binding similar to sunitinib. It is metabolized in the liver by CYP3A4 and UGT1A9, with a survival of 30 hours. It is used as a third-line treatment for resistant GIST—the effect of targeted therapy results in apoptosis of GIST cells and tumor stabilization or destruction. Pazopanib is currently being treated with imatinib and sunitinib, which has shown improvement with survival of 3.4 months and 2.3 months with imatinib and sunitinib together. Avapritinib is used as a third-line treatment

DOI 10.5281/zenodo.14744305

and has been compared with regorafenib. There is no evidence of improvement with one or the other, a better response has only been seen in patients with a mutation in PDGFRA exon 18 D842V who are resistant to other tyrosine kinase inhibitors. It was compared in a study with imatinib, sunitinib, and regorafenib; it was shown that with Ripretinib there is an increase in survival (6.6 months vs 1 month) and it was increased up to 3.7 months in patients with double dosing (2x150 mg). It continues under investigation, there are reported cases of resistance due to mutation in exon 13 [26].

In a case report study in Japan, a patient is mentioned who uses pimitespib, a therapy directed at an inhibitor of the new heat shock protein 90 (HSP90), which is responsible for the conformation, function, and activation of cancer-related proteins such as KIT and PDGFRA. The inhibition of HSP 90 generates a downregulation of multiple signaling pathways in tumor cells that lead to anti-carcinogenesis. It has been used in phase II studies in those who fail or do not tolerate sunitinib and regorafenib. The case presents a 55-year-old female patient, with PDGFRA D842 positivity, who was followed up without chemotherapy, and after 7 years she presented peritoneal recurrence in the upper right abdomen and pelvic cavity. Imatinib was administered for 10 months, sunitinib for 3 months and regorafenib for 5 months with poor improvement. Therefore, pimitespib 160 mg/day was used for 5 consecutive days, then every 2 days for 21 cycles, with only diarrhea as a side effect. For the first 8 months, the tumor stabilized and the effect was slow. However, in the ninth month, there was a partial response with a reduction of 32.7%. At 24 months of treatment, a decrease in tumor size was found. At the time of failure, palliative treatment was decided. It was concluded that it may improve the response in patients with no response to conventional treatment and with PDGFRA D842V alteration [29,30].

Follow-up of this type of patient should be carried out considering the degree of risk. In high-risk patients, follow-up is with an abdominal CT scan or magnetic resonance imaging, every 3-6 months for 3 years, during adjuvant therapy. During adjuvant therapy, every 3 months for 2 years, and subsequently every 6 months for 5 years until the end of adjuvant therapy and after that, every year for 5 years. In patients with low-risk tumors, CT or MRI is recommended, every 6-12 months for 5 years. In very low-risk patients, follow-up with X-ray exposure is not required, so magnetic resonance imaging may be an option [31,32].

Conclusion

GISTs are tumors that can develop randomly or as a component of a hereditary disease. The natural history of these tumors is variable depending on histological characteristics, however there are negative prognostic variables are young age, tumor size, high mitotic index, aneuploidy, and tumor location (Gastric tumors have a better prognosis than those located in the intestine). For an accurate diagnosis and differentiation between GISTs and other tumors with the same location, histopathological and immunohistochemical tests are necessary. These tests are very important since therapeutic management is different depending on the histology of the tumors. Patients with advanced GISTs require evaluation of the mutational status for appropriate, and targeted chemotherapy. Adequate treatment can improve patient prognosis and epidemiological indicators, such as morbidity and mortality. Although it is not a common pathology, it should be considered among the possible diagnoses for a gastrointestinal tumor.

Conflicts of interests

The authors have stated that no entity has provided financial support for the work that was submitted. No financial ties exist with any organizations that might be interested in the work that was submitted.

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 DOI 10.5281/zenodo.14744305