Gastric GIST with progressive mitotic index

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Abstract

Background. Gastrointestinal stromal tumors (GISTs) account for less than 1% of gastrointestinal tumors; they are the most common mesenchymal neoplasms of the gastrointestinal (GI) tract. GISTs are usually located in the stomach, but can occur anywhere along the gastrointestinal tract. GIST ranks third as histology after adenocarcinomas and lymphomas among the gastrointestinal tract. **Case presentation.** The patient, aged 58 years, is transferred from the Gastroenterology Clinic with symptoms of stenosis and hemorrhage from a endophytic submucosal tumor located on the posterior gastric wall, under the eso-gastric junction, objectified endoscopically and CT scan. Laparoscopic wedge resection was performed with three linear Endo-GIA staplers. The evolution was favorable. After 7 months (without chemotherapy because pTNM was T1NoMo), the patient is sent back by the gastroenterologist for „CT scan: perigastric lymphadenopathies”. The patient was operated laparoscopically converted. We found 10 tumors with typical malignant GISTs 3-10 cm diameter, on the peritoneal serosa: in the right subhepatic space, perigastric, left interhepato-phrenic, hepato-gastric; these were excised R0; with simple evolution. The immuno-histo-chemical examination specifies the diagnosis of GIST at the first and the second operation (DOG1, CD117, CD34-positively in tumor). Ki 67 was 15% in the tumor and the mitotic index <5/5 square mm at the moment of the first operation but in the metastatic tumor at the reintervention Ki 67 was 80% and mitotic index >5/5 square mm. **Discutions.** GIST tumours can be classified into low-risk and high-risk categories of recurrence depending on size, location, capsule rupture and mitotic activity. Disseminated metastases in the abdominal cavity are the most common clinical manifestations of malignancy. Complete surgical resection is recommended if bleeding or other symptoms are present. Tumour perforation, spontaneous or produced at the time of surgical resection, should be recorded because it has a high negative prognostic value due to peritoneal contamination. The average survival rate in localized disease is 5 years but in metastatic or recurrent disease is about 10-20 months. **Conclusion.** Complete excision of residual metastatic lesions has been shown to be associated with a favourable prognosis, provided that the patient responds to imatinib treatment; resection of tumour recurrence is accompanied by an average survival of 15 months. Gastric GIST recurrence risk depends of localisation, tumor size, mitotic index and capsular rupture.

Keywords: : Gastric GIST, Resection R0, Follow-up, Imatinib.

Introduction

Gastrointestinal stromal tumours (GISTs) were initially thought to originate from mesenchymal cells of the gastrointestinal tract (GIT) (1,2). Gastrointestinal stromal tumours (GISTs) account for less than 1% of gastrointestinal tumours, although they are the most common mesenchymal neoplasms of the gastrointestinal tract. Kindblom and associates in 1998 found that these tumours originated in the interstitial cells of Cajal (3)

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Received: January 10, 2021; **Accepted:** February 20, 2021;

Published: Mars 05, 2021

Citation: Bradea C., Lupaşcu C., Munteanu Valentina, Ciobanu Delia, Cucu Cătălina, Bejan V., Vasilescu A.: **Gastric GIST** with progressive mitotic index. Journal of Surgery [Jurnalul de chirurgie]. 2021; 17(1): 46 - 51 DOI: 10.22551/JSURG.2021.01.06

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GIST ranks 3rd as histology after adenocarcinomas and lymphomas among the histological types of tumours of the gastrointestinal tract. Hirota and colleagues found that these tumours express the CD117 antigen (C-Kit)-functional mutation responsible for activating the tumour growth (4). Historically, are classified as leiomyomas or sarcomas because smooth muscle characteristics at microscopy.

GISTs are considered rare tumours, discovered by chance. The true prevalence is unknown. Traditional chemotherapy and radiation are not effective for GIST, surgical resection been the treatment of choice (5,6). The advent of immune-histochemistry show that the antigens expressed by these tumours are bound to neural crest cells. Mazur and Clark, Schaldenbrand and Appleman in 1980' describe "stromal tumours" as a separate entity. Kindblom reported in 1998 year that the source cell of GIST is a pluripotent mesenchymal stem cell programmed to differentiate into the Cajal interstitial cell. These are GI pacemaker cells found in the muscle itself and around the meningeal plexus and are largely responsible for gastrointestinal motility.

With the discovery the treatment changed dramatically. Further studies found that Cajal interstitial cells express the KIT gene and are dependent on stem cell factor, which is regulated by KIT kinase. Imatinib mesylate, a tyrosine kinase receptor inhibitor (TKI), is used as adjunctive or neoadjuvant therapy to improve GIST-associated morbidity and mortality. Sunitinib and

5,000 new cases of GIST are diagnosed annually in the United States. Population studies in Iceland, the Netherlands, Spain and Sweden report annual incidence rates ranging from 6.5 to 14.5 cases per million. Outcomes in patients with GIST are dependent on the clinical presentation and histopathological features of the tumour. The overall 5-year survival rate varies from 28-60%. This can be stratified for patients with localized primary disease and those with metastatic or recurrent disease. The average survival rate in localized disease is 5 years, while the average survival rate in metastatic or recurrent disease is about 10-20 months. Higher risk GISTs are associated with complications such as bleeding, obstruction and perforation. Tumours can be classified into low-risk and high-risk categories of recurrence depending on size, location, and mitotic activity.

Case Presentation

The patient, aged 58 years, is transferred from the Gastroenterology Clinic with symptoms of stenosis and hemorrhage from a endophytic tumor located on the posterior gastric wall, under the eso-gastric junction, objectified by endoscopy and CT scan.

Laparoscopic wedge resection was performed with three linear Endo-GIA staplers. The evolution was favorable (Fig. 1).

Fig.1:Gastric GIST-Laparoscopic resection

After 7 months (without chemotherapy because of T1NoMo), the patient was sent back by the gastroenterologist for „perigastric lymphadenopathy at CT scan”. It was operated laparoscopically converted with resection R0 of 10 typical malignant GIST 3-10 cm diameter on the peritoneal serosa:in the right sub hepatic

space, perigastric, left interhepatophrenic, hepatogastric (Fig.2).

Fig.2-Peritoneal metastases at 7 months after primar GIST resection without chemotherapy

The evolution was simple. The immuno-histo-chemistry specifies the diagnosis of GIST at the first and the second operation (DOG1, CD117, CD34-positively in tumor). Ki 67 was 15% in the tumor and the mitotic index

<5/5 HPF at the moment of the first operation but in the metastatic tumor at the reintervention Ki 67 was 80% and mitotic index >5/5 HPF (Fig.3).

Fig.3.a-High Mitotic Index

Fig.3.b-Spindle Cells

Fig.3c-CD-34

Fig.3.d-CD-117

Fig.3.e-DOG1

Discutions

GIST are the most common mesenchymal tumours specific to the gastrointestinal tract, generally defined as KIT positive tumours (CD117) with a characteristic set of histological features (Miettinen). GIST can occur anywhere in the gastrointestinal tract. They are submucosal lesions, which most often grow endo/exo-phytically; the size varies from 1-40 cm in diameter; 50-70% are located in the stomach. Other locations: jejunoileal

(20-30%), colo-rectal (5-15%), oesophagus (<5%), pancreatic, epiploic or mesenteric.

Most GISTs are associated with mutations in exon 11 of the c-KIT proto-oncogene which leads to c-Kit auto-phosphorylation. This causes an intracellular signalling cascade to proliferation or to apoptosis. The c-KIT is located on the chromosome 4q11-12 and encodes KIT, a transmembrane tyrosine kinase. KIT activation is initiated when the stem cell factor binds to the extracellular domain of the c-Kit. This result in homodimerization of normally inactive c-Kit (14).

Soreide analysed 29 studies with 13,550 patients from 19 countries with GIST between 2000-2014 (15) with median age 65 years, male/female 1: 1. The highest incidence rates (19-22/million/year) were observed in Hong Kong, Shanghai, Taiwan and Norway and the lowest in China's Shanxi Province (4.3); 18% of GISTs were discovered by chance. GISTs were found in the stomach (56%), small intestine (32%), colo-rectal (6%), oesophagus (0.7%) and other locations (5.5%)(15). About 10% to 30% of GIST progress to malignancy's that occur outside the stomach are associated with a higher malignant potential (16). Exophytic growth is observed in 79% of GIST (17).

A small minority of GISTs are associated with hereditary syndromes. 90% of patients with these mutations are at risk of being diagnosed with GIST at age 70.

GIST is one of several malignancies that can occur with type 1 neuro-fibromatosis (NF-1), gliomas and neuro-fibromas. Carney Triade, mainly in young women, consists of GIST, pulmonary chondromas and extra-adrenal paragangliomas.

Tateishi studied histologic tumour grade and mortality rate in patients with low-grade (n = 44) and high-grade (n = 25) GISTs by CT scan: tumours >1.1 cm had high grade histology, irregular borders, invasion to adjacent organs, hepatic or peritoneal metastases, associated with high mortality. In conclusion, evolutive CT scan assess tumour size and metastasis and the treatment response to neo/adjuvant therapies.

75% of GISTs are detected < 4 cm in diameter, asymptomatic. They are frequently diagnosed accidentally during endoscopic/radiological/surgical procedures for bleeding or obstruction.

PET scans with 2- [F-18] -fluoro-2-deoxy-D-glucose, together with CT scan, provide useful information in tumour staging, identifying areas of necrosis, to differentiate benign from malignant and to determine the effectiveness of adjuvant therapies (18,20).

Fine Needle Aspiration Endoscopic Ultra Sound guided biopsy confirm GIST before preoperative therapy by histo-pathology and immune-chemistry. GISTs have three different histological types: spindle (70%), epithelioid (20%) or mixed (10%). They are often misdiagnosed as leiomyoma or leiomyosarcoma before immunohistochemical analysis (3). A recent analysis of 70 cases of GIST showed positive expression of CD117 and DOG-1 in 95.71% and 88.57% of cases, respectively (21). The literature suggests that DOG-1 appears to be more sensitive and specific than CD117 (DOG1 is a calcium-dependent chloride channel activating receptor protein and is expressed in GISTs independent of the type of mutation).

Many classification systems have evolved over the years, but neither has proven to be superior to the other. In 2002, Fletcher and colleagues collaborated to create the NIH classification, the first GIST classification. It

determined the risk of recurrence in very low, low, intermediate, and high-risk, examining the size and mitotic activity of the tumour (22). They concluded that tumours > 5 cm in diameter plus a mitotic activity greater than 5/50 high power fields (HPF) and tumours > 10 cm at any mitotic rate have a higher risk of recurrence, requiring neoadjuvant or adjuvant drug therapy. (22).

In a long-term follow-up of 1765 patients with gastric GIST, Miettinen reported that the metastasis rate was 86% for tumours > 10 cm, with a mitotic index > 5 mitoses / 50 HPFs, while tumours with the same size with a mitotic index < 5 mitoses / 50 HPF have a relatively low metastatic rate of 11%. In a subsequent report involving 906 patients with intestinal GIST, tumours > 10 cm with a mitotic index ≤ 5 mitoses / 50 HPF had a metastatic rate of 50%. Therefore, tumour location was also included in guidelines. Intestinal GISTs > 5 cm, independent of mitotic rate, have a moderate risk of metastasis; all > 5 mitoses/50 HPF have a high risk of metastases and all < or = 5 mitoses/50 HPF have a low risk of metastasis (23).

Clinico-pathologic features, including NIH and modified schemes, were retrospectively analysed for 289 patients with localized GISTs. The "risk level I" group had < or = 5 cm, < 5/50 HPF, the intermediate as "risk level II" (< 5 cm, 6-10 mitoses/50 HPFs or 5-10 cm, < 5/50 HPF), "risk level IV" group > 5 cm and > 10/50 HPF and the rest is "risk level III". The 5-year rate of Disease Specific Survival (DSS) for all 289 patients was 82% (risk levels I to IV were 100%, 96%, 67%, and 25%). The higher risk level represented the strongest independent adverse factor followed by mixed/epithelioid histology and older age (24).

The gold standard treatment for GIST is laparoscopic wedge resection for tumour less than 5 cm, located in the stomach and small intestine. Chen and associates analysed 58 GISTs: 16 cases (27%) with laparoscopic resection (LR) and 42 cases (73%) with open resection (OR). Recurrence: 1c with LR (33 months follow-up) and 2c with OR (in 40 months). The LR group had a normal diet earlier, shorter postoperative hospitalisation, and required less pain management. Postoperative morbidity was 6.3% in LR group and 19% in the OR group (25).

Wu reviewed 57 patients from 1995-2002 y, with follow-up of 18 months, with mean age 61y and 50% women; 28 (49%) patients with OR curative resection, and the other 29 (51%) were treated post-surgically with imatinib for metastatic disease (n = 26) or adjuvant therapy (n = 3). 22 p (79% with curative intent) had negative margins of resection, 3p had metastases that were completely resected with the tumour and 2p had successful resection after neoadjuvant imatinib therapy. CD117 staining was positive in 96% of tumours, and metastasis was detected in 17 patients at the time of surgery. Twenty-six patients with metastatic disease were treated with imatinib and tumour regression was observed in 22 p at 19 months. In total, 23 p (40%) were alive without disease, 22

p (39%) were alive with disease, 7 p died and 5 p were lost to follow-up. They concluded that surgical resection with negative margins is the curative treatment for GIST. If there is a metastatic disease, then imatinib should be recommended as a targeted therapy in combination with surgery (6).

Patients with high-risk categories for metastasis must have a follow-up with serial CT scans every three months for five years (7,30). Patnaik analysed 42 p with GIST: metastasis rate 59.5% (n = 25), age 50 y, male/female 2: 1; 22 p (52.3%) had metastasis and 3 p (7, 1%) developed metastases after resection of the primary tumour (26).

Conclusion

GISTs are rare among gastrointestinal neoplasia. Outside the stomach they are associated with a higher malignancy potential. Usually they are found incidental (without symptoms).

GIST patients can present nausea, vomiting, abdominal distension, abdominal pain or peritonitis.

GISTs are identified by abdominal ultrasound, CT scan, MRI and PET+/-CT.

The pathology of GISTs consist of spindle cells, epithelioid cells or mixed cell types. GISTs most commonly stain positive for CD117 and DOG-1.

GISTs are staged using the TGM system, which determines that grade and metastasis are the best predictors of prognosis. The grading systems of GISTs are used to determine the effectiveness of imatinib as neoadjuvant /adjuvant therapy.

Laparoscopic surgical resection of GISTs with adjuvant imatinib 400 mg daily is the gold standard. If the tumour is unresectable then neoadjuvant imatinib 400 mg daily followed by resection is recommended. Metastasis are very common and can be seen in the liver and peritoneum and are treated as high risk GISTs.

The risk of malignancy potential and recurrence is calculated based on tumour size, mitotic rate, location and perforation. TKIs are recommended for high risk GISTs (imatinib 400 mg/day, sunitinib for CD117 exon 9, 13, or 14 mutations, while ponatinib is used for CD117 exon 17 mutations and regorafenib in highly refractory tumours).

All GISTs have been considered to have some malignant potential, but this hypothesis is now seriously challenged by studies indicating that microscopic gastric GISTs that are common in the general population probably have little or no malignant potential. The National Institutes of Health (NIH) consensus classification system, based on tumour size and mitotic count, is commonly used to assess patient prognosis after surgical resection by large retrospective cohort studies from several countries. Patients with high-risk GIST (44%) have substantially poorer outcome than those with intermediate-risk (24%) or low/very low-risk (32%). Gastric GISTs (58% of all GISTs) have a lower risk of recurrence than non-gastric

tumours of the same size and mitotic count. Tumour rupture confers clearly increased risk. Patients with certain no gastric tumours (2.1-5 cm and > 5 mitoses /50 HPF or 5.1-10 cm and < or = 5 mitoses/ 50 HPF) and those with tumour rupture are proposed to be included in the NIH high-risk category. High-risk patients defined by the proposed modified system have more than 15% to 20% risk of disease recurrence. The proposed system may be useful in identifying which patients might potentially benefit from adjuvant therapy (27).

Competing interests: The authors declare none. **Patient consent:** The patient consent was obtained.

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