

Gastrointestinal stromal tumor (GIST): An infrequent observation

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Abstract

Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal neoplasms of the gastrointestinal tract. Historically, these lesions were classified as leiomyomas or leiomyosarcomas, but the actual cell of origin of GISTs is a pluripotential mesenchymal stem cell programmed to differentiate into the interstitial cell of Cajal. These advances have led to the classification of GISTs as an entity separate from smooth muscle tumors. The case of 39-year-old male patient with the diagnosis of gastrointestinal stromal tumor of the small intestine is presented. The clinical manifestations, epidemiology and immunohistochemical diagnostic features are discussed. Finally, differential diagnosis and therapeutics are exposed. We stand out the importance of the surgical management and Imatinib (Glivec) in these tumors.

Key words

Gastrointestinal stromal tumor, small intestine, therapeutics.

INTRODUCTION

The term "Gastrointestinal Stromal Tumor" (GIST) was introduced by Mazur and Clark in 1983 (1) and was accepted worldwide by the OMS in the international classification of tumors in 1990. It is estimated that the annual incidence of GISTs is 10 to 20 cases per million inhabitants. Out of these 20% to 30% are malignant. Although they represent only 2% of the neoplasias in the digestive tract, they are the most frequent mesenchymal neoplasias of the gastrointestinal tract (2). These numbers may vary after revision of the new classification criteria. Currently reported as GISTs, they were formerly included in another variety of gastrointestinal tumors. When they were first described by Golden and Stout, this group of mesenchymal lesions was considered to be of muscular origin. Thus they received different names including leiomyomas, cellular leiomyomas, epithelial leiomyomas,

leiomyoblastomas, bizarre leiomyoma and leiomyosarcomas (3). Nevertheless, it is now known that their origins lie in mesenchymal by-products such as the progenitors of fusiform and epithelial cells (1). On the whole, among the various histological types of tumors in the gastrointestinal tract, GISTs hold a distant third place in prevalence after the adenocarcinomas and lymphomas (1).

In 1998, Kimdbloom and associates reported that the real origin of the GISTs is in the mesenchymal pluripotency mother cell programmed to differentiate itself into the *interstitial cell of Cajal* (4). The interstitial cell of Cajal functions as a pacemaker for the intestine by coordinating peristalsis. It requires normal expression and function of the tyrosine kinase KIT receptor for its development (5, 6).

Almost all cases of GIST are considered to result from somatic mutations in the proto-oncogene *c-kit*, with rare

KIT-negative cases associated with hereditary syndromes, such as in the case of neurofibromatosis type I (7, 1).

The objective of this work is to present the case of a GIST located in the small intestine of a 39 year old patient. This type of clinical data represents a very infrequent case for this institution.

THE CLINICAL CASE

A 39 year old male patient with no family history worth mentioning was hospitalized due to abdominal pains of a vague colic nature. The pain became acute. Located in the right hypochondrium, it irradiated and banded to the back. It was accompanied by nausea, occasional vomiting, constipation and loss of 12 kilograms over 2 months.

Physical examination

General condition: The patient was weak and slightly dehydration, but alert and conscious.

Cardiopulmonary apparatus: The patient's breathing rate was 20 br/min with normal pulmonary auscultation in both hemithoraxes. His cardiac rhythmic tone had good intensity, and there was no heart murmur. His central heart rate was 100 b/min, and his blood pressure was 120/70 mm Hg.

Abdomen: His abdomen was soft, but not tender. It was painful when deeply palpated on the right hemi-abdomen. At the side an abdominal polylobulated mass was felt. It was slightly moveable, measured 20 cm in diameter. It was discreetly painful. On the right lobe of the liver, a unique, but not painful, 3 cm irregular nodular lesion was felt. The rest of the abdomen was negative. There was nothing to report about the examinations of other systems, including rectal tract and the background of the eye.

Analytical study and evolution

Hb: 11 g/dL, hematocrit: 35%, Leukocytes: $5,6 \times 10^9/L$ with normal differential formula. Globular sedimentation speed: 112mm/1ah. LDH: 515 U/L ($N < 400 U/L$). Glycemia, creatinine, pancreatic enzymes, ions, uric acid: normal. Hepatic enzymes were normal, except for the alkaline phosphatase: 435 U/L ($N < 190 U/L$). Alpha fetoprotein: 6 ng/mL ($N: 0-8,5 ng/mL$). HIV and VDRL: not reactive.

Electrocardiogram: sinus tachycardia. *X-ray of the thorax:* elevation of the right hemidiaphragm. *Abdominal ultrasound:* complex image of a mass, predominantly solid, of 25 x 18 cm, with fine handle-like expansions, enlarging and distending segments of the small intestine. A 3, 5 cm nodular image on the right hepatic lobe, of possible metastatic etiology, a biopsy of the lesion is suggested. *Computerized axial tomogra-*

phy (CAT scan) of the abdomen: Hyper dense mass of 26x18 cm that displaced the small intestine; a metastatic lesion was found at the level of the right hepatic lobe. It measured 3.5 to 4 cm. The rest of the exam was without alterations. *Cytology by aspiration with a thin needle* was carried out, preceded by ultrasound of the tumoral mass. The patient tested positive for fuso-epithelioid neoplastic cells of a low cytological degree, an immunohistochemical study was carried out on the cytological layout, which tested positive for CD117, confirming the diagnosis of a GIST. In the same manner, cytology was carried out on the hepatic metastasis obtaining the same results (Figures 1 and 2).

The patient was submitted to an exploratory laparotomy which encountered a tumoral mass of 25x6x7 cm. The tumor affected the sides of the small intestine with handle-like expansions with which it was integrated. Exeresis of the tumor was performed revealing *high degree fuso-epithelioid GIST of the small intestine*, which was confirmed by immunohistochemical study of: CD117*, CD34*, S-100*, desmin* (Figures 3-6). Treatment was initiated with Imatinib (STI-571-Glivec). Daily doses were 400 mg, administered for a period of 6 months. Up to now, periodic checkups of the patient have shown regression of the symptoms, but there has been neither any report of recurrences nor any new metastasis during this time.

DISCUSSION

GISTs frequently appear in the elderly and people over 50. The reported average age in long series was in the range between 55 and 65 years of age with similar proportions for men and women. However, when GISTs appear as malignant lesions they can turn up at earlier ages (7). Our patient was a 39 year old male.

These tumors are occasionally found in an incidental manner in the serous membrane of the small intestine and stomach during surgery for some other cause, gastroscopies, or x-ray inspections (8).

In approximately 95% of these patients, GISTs appear as a solitary primary tumor: However, in 10% to 40% they appear as invasive tumors in other organs, revealing a close relationship between anatomic location and the prognosis. Small tumors in the small intestine have worse prognoses than large tumors in the stomach (2, 3, 7). Gastric GISTs may form part of the Carney syndrome (stromal gastric epithelioid tumors, pulmonary chondroma, and extra-adrenal paragangliomas) (1, 9).

Clinic presentation varies according to the location, growth pattern, and size of the tumor. Nevertheless, within the non-specific symptomatology these reveal, some studies have shown some widespread symptoms including pain in 40% to 70% of cases, hemorrhaging in 20% to 50%

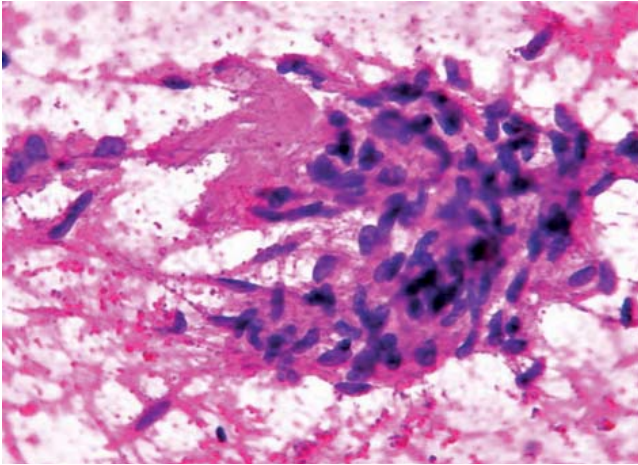


Figure 1. Cytological layout of a hepatic node. Observe the fusio-epithelioid cells of low cytological degree forming conglomerates or crowds (H/E 40x)

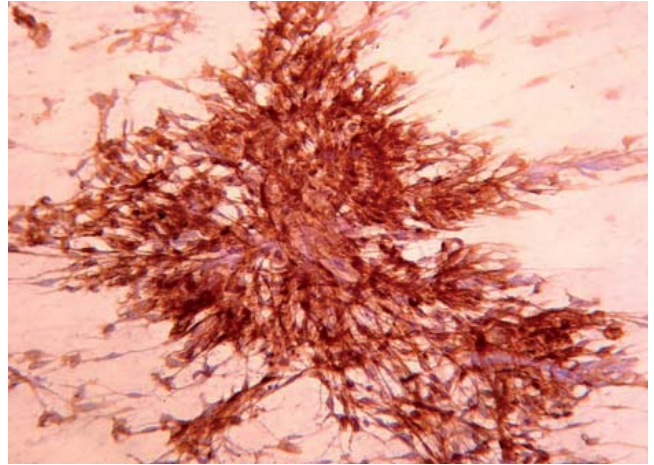


Figure 2. Immunohistochemical study. Observe a field of the cytological layout of the liver node, intensely positive to CD117.

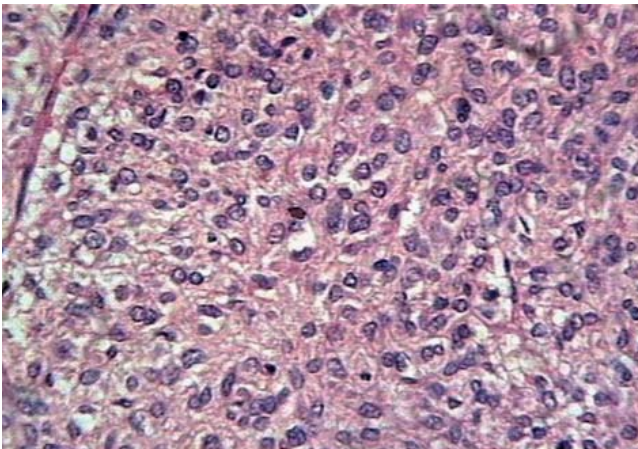


Figure 3. Microphotography of a field of the tumor in the small intestine, revealing an epithelioid pattern.

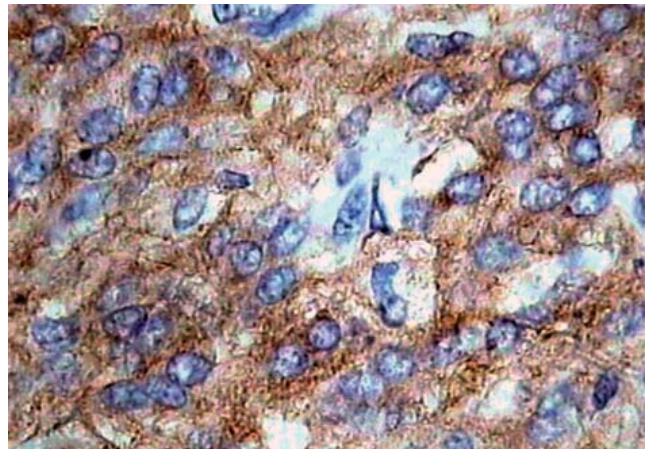


Figure 4. Previous image, intensely positive to CD117.

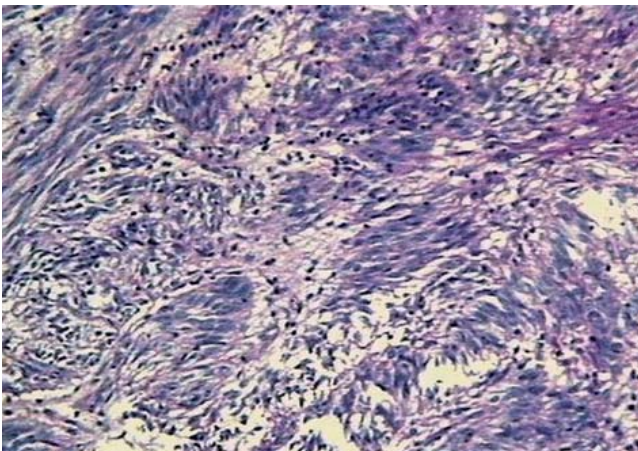


Figure 5. Histology of another area of the tumor, revealing a typical palisade pattern (H/E 40x).

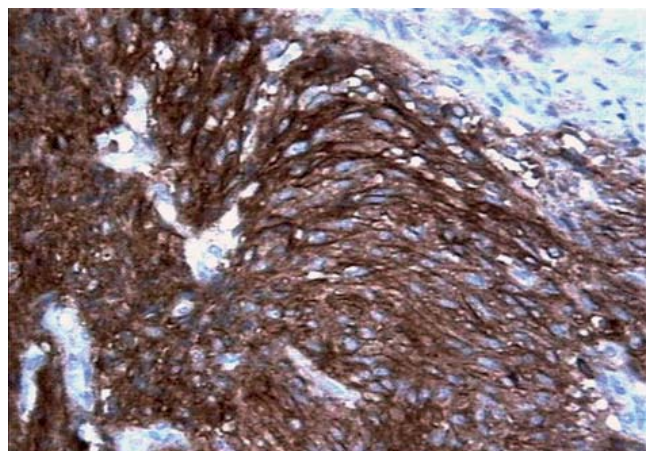


Figure 6. Previous image, showing positive to CD117.

of cases and palpable masses in 20% of cases. The first two are the most persistent signs, and both were present in our case (An appearance also consistent with obstruction and perforation) (11). The most aggressive GISTs can appear with abdominal dissemination and/or hepatic, pulmonary, and peritoneal metastasis (10, 11). In our patient's case, it was a unique hepatic metastasis of 3,5 cm.

These tumors are located in the stomach (50-60%), small intestine (20%), large intestine (10%), esophagus (5%), and occasionally in the omentum, mesentery, and retroperitoneum (around 2%) (12). Their macroscopic aspects depend on their size which varies between 0.8 and 3.8 cm. Microscopically it is possible to distinguish three categories: tumors with fusiform cells (77%), epithelioid tumors (8%), and mixed tumors (15%) (3,5,7). In our patient, the tumor was located in the small intestine, measured 25x16x7 cm and was made up of fusiform cells.

In recent years an important change in the interpretation of these pathologies has been established, principally due to the contributions of immunohistochemistry, electron microscopy, molecular biology, and histogenesis studies. (13). GISTs may reveal a great number of antigens, the most frequently occurring being the CD117, which is present in practically 100% of all cases. In fact, the only cells of the gastrointestinal tract which normally evince CD117 are the interstitial cells of Cajal. The reason is believed to be that they share a common precursor (4, 14). It is recommended to simultaneously use other markers the diagnosis of GIST including CD34, actin, desmin, S-100, enolase, and chromogranin (13, 14). Several of these were tested for in our patient.

Imaging techniques are useful in the diagnosis of GISTs and their metastasis. Endoscopic images show lumps that protrude from the walls towards the light source, on occasion with signs of ulceration and hemorrhaging (15). The presence of a mass >4 cm, with irregular edges, echogenic cores, and cystic areas is very suggestive of a GIST (2, 8, 10, 12, 3). This was in fact observed in this particular case. The CAT and MRI are essential for assessment of both the primary tumor and the presence of metastasis (2, 3).

Differential diagnosis must take into account fibrohistiocytic neoplasms, the peripheral nerve sheath, the smooth muscle, Kaposi's sarcoma, and slightly undifferentiated adenocarcinomas (16). Prognosis depends on factors that interrelate amongst themselves. These include age, presence of metastasis, histological characteristics, size of tumor, number of mitosis, immunophenotype, ploidy and genetic mutations (9, 12).

Primary treatment is complete surgical resection (17) which was performed on this patient. If the tumor ruptures inside the abdominal cavity while removal is being attempted,

relapse is certain. For this reason laparoscopy is contraindicated (17).

Imatinib mesilate (STI-571-Glivec) is a medicine produced for the treatment of chronic myeloid leukemia. BCR-ABL is a deviant enzyme that causes leukemia in the blood cells in a way analogous to the way KIT develops GISTs in the cells of Cajal (18). Gleevec was produced to interfere with the chemical reaction by means of which ATP provides energy to BCR-ABL enzymes. It is mainly employed in regard to unresectable tumors (19). In our case, apart from surgery, a daily dose of 400 mg of Gleevec was used for six months, from the day following the surgery to the present moment. The patient has been found to be free of symptomatology or metastasis through frequent analytical and imaging check-ups required by the adverse reactions of the medicine.

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