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Gastrointestinal Stromal Tumors - Diagnosis and Surgical Treatment

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Rezumat

Tumorile stromale gastrointestinale - diagnostic și tratament chirurgical

Tumorile stromale gastrointestinale (TSGI) sunt cele mai frecvente tumori cu origine mezenchimală ale tubului digestiv, anterior fiind clasificate ca leiomioame, leiomiosarcoame, leiomioblastoame sau schwanoame. Actual sunt recunoscute ca o entitate de sine stătătoare, cu originea în celulele intrestițiale mezodermale Cajal, celule ce supraexprimă proteina c-kit (receptor de tirozin kinază). Diagnosticul definitiv este stabilit prin imunohistochimie, peste 95% din TSGI fiind pozitive pentru CD117. În ciuda progresului major al chimioterapiei, tratamentul de elecție rămâne cel chirurgical și implică rezecția completă a tumorii. Evoluția acestor tumori este imprevizibilă iar prognosticul depinde de localizare, dimensiunea tumorii și indicele mitotic. Tumorile benigne au prognostic excelent după tratament chirurgical cu supraviețuire de peste 90% la 5 ani pe când tumorile maligne, rezistente la radioterapie și chimioterapie au prognostic sumbru chiar și după rezecție, supraviețuirea medie fiind de 1 an. Am studiat un lot de 15 pacienți diagnosticați cu TSGI în cadrul Clinicii de Chirurgie Generală a Spitalului Clinic de Urgență "Prof. Dr. Agrippa Ionescu" între anii 2003 - 2013, urmărind particularitățile de prezentare, diagnostic și tratament, cu evidențierea factorilor de prognostic în raport cu datele din literatură disponibile.

Cuvinte cheie: tumori stromale gastrointestinale (TSGI), tratament chirurgical, prognostic

Abstract

Gastrointestinal stromal tumors (GIST) are the most common mesenchymal tumors of the gastrointestinal tract, previously classified as leiomyomas, leiomyosarcomas, leiomyoblastomas or schwannomas. They are now recognized as a distinct entity with origin in the mesodermal interstitial cell of Cajal, cells that express the c-KIT protein (tirozine kinase receptor). The definitive diagnosis is established by immunohistochemistry, more than 95% of GISTs being positive for CD117. Despite the major progress of chemotherapy, the treatment of choice is surgery, and it implies the complete resection of the tumor. The evolution of these tumors is unpredictable and the prognosis depends on localization, tumor size and mitotic index. Benign tumors have an excellent prognosis after surgery, with a 5 year survival of 90%, while malignant tumors resistant to radiotherapy and chemotherapy have a dismal prognosis even after surgical resection, with a median survival of 1 year. We studied a group of 15 patients diagnosed with TSGI in the Surgery Clinic of the "Prof. Dr. Agrippa Ionescu" Clinical Emergency Hospital, between 2003 and 2013, following the particularities of presentation, diagnosis and treatment, with focus on the prognostic factors according to available literature data.

Key words: GIST, surgical treatment, prognosis

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Introduction

GISTs are very rare neoplasms of the gastrointestinal tract, accounting for 0.1-3% of all gastrointestinal tumors, being at the same time the most common non-epithelial digestive tumors (1,2,3). The term was introduced by Mazur et al (4) in 1983, when discussing tumors of neurogenic or myogenic differentiation that lacked the features of Schwann cells and ultrastructural characteristics of smooth muscle cells. Furthermore, the discovery in 1986 of the oncogene c-KIT which encodes a transmembrane tyrosine kinase receptor and mice with mutations in the KIT gene lacked the interstitial cells of Cajal, pointed to the origin of the GISTs (5,6,7). These pacemaker cells that form the interface between the autonomic innervation and smooth muscle of the bowel have immunophenotypic and structural characteristics of both smooth muscle and neural tissue and so do GISTs. The elegant research of Hirota et al showed that c-KIT mutations play an important role in the pathogenesis of GISTs by gain of function of the enzymatic activity of the KIT tyrosine kinase, expressing the KIT protein (CD117), hence a reliable phenotypic marker (8,9).

More than 95% of GISTs are positive for CD117. In 60-70% of these patients,immunohistochemistry for CD34 is also positive (10,11). A small proportion of GISTs (10-15%) have no detectable KIT mutations, in these cases DOG-1 can be used for diagnosis (12).

The median age at diagnosis is 60 years, without significant predilection for either sex. Familial GISTs are autosomal dominant (13).

GISTs can develop anywhere from the esophagus to the rectum. The stomach (60%) and the small intestine (30%) are the most common locations. Up to 30% of GISTs have a malignant behavior by infiltration and metastasis (12).The metastatic pattern is intra-peritoneal and to the liver. Lymph node involvement is uncommon (13,14,15). The estimated risk of GIST progression was first classified by Fletcher in 2002 and extended by Miettinen taking into account besides tumor size and mitotic index also tumor localization – i.e. small intestine GISTs have a higher rate of malignant behavior than gastric GISTs (9,16,17) - *Table 1*. A mitotic rate over 5 per HPF results in a metastatic rate over 50% (18).

Complete surgical resections still remains the single curative form of treatment. Regional lymphadenectomy is not generally required and organ-sparing resections are oncologically appropriate (32). The main goal should be tumor resection with free margins and an intact pseudocapsule. Complete resections offers a 5 year overall survival of 42% while incomplete resection offers less than 10% (19). When GISTs infiltrate surrounding organs, en bloc resection should be taken into account. GISTs are fragile, special care should be taken while handling the tumor. It is imperative to avoid intraperitoneal rupture or bleeding, the risk of recurrence in these cases being as high as 100% (20,21).

The year 2000 brought into perspective the tyrosine kinase inhibitor imatinibmesylate – (Gleevec®, Novartis, Basel, Switzerland) that soon became the first line of treatment for inoperable or metastatic GIST (22). Imatinib inhibits proliferation and survival of tumor cells (23). Currently, Imatinib mesylate and several other tyrosine kinase inhibitors are used both as neodajuvant therapy to facilitate R0 resections and as adjuvant therapy to decrease the risk of postoperative recurrence in high-risk tumors (24,17).

Matherial and Method

We conducted a retrospective study on 15 admitted patients, diagnosed with GISTs that underwent surgery in the General Surgery Clinic of "Prof. Dr. Agrippa Ionescu" between January 2003 and July 2013. We studied the epidemiologic factors, the clinical presentation, the diagnostic workup, the type of surgical resection and histological and immunohistochemical reports, highlighting particular aspects.

Results

Our series included 15 patients admitted between January 2003 and July 2013.

The median age at the time of diagnosis in the studied lot was 53.4 years (range 28 – 75). Sex distribution was almost equal: 8 men with a median age of 58.3 years (range 35 – 75) and 7 women with a median age of 55.4 years (range 28 – 72). With 5 cases diagnosed until 2010 and 10 cases from 2010 to July 2013 we find an interesting rise in number of cases.

The localization of the tumors was in order of frequency the following: stomach 9 (60%), small bowel 5 (33%) – 2 ileal tumors (13%) and 3 jejunal tumors (20%) and one hepatic

Table 1. *Risk of clinical progression according to Miettinen (17)*

Mitotic rate	Tumor size (cm)	Stomach	Jejunum / ileum	Duodenum	Rectum
≤5/50 HPF	≤2	None	None	None	None
	>2≤5	Very low	Low	Low	Low
	>5≤10	Low	Moderate	High	High
	>10	Moderate	High		
>5/50 HPF	≤2	None	High	n.a.	High
	>2≤5	Moderate	High	High	High
	>5≤10	High	High	High	High
	>10	High	High		

GIST left lobe – segment III (6.6%) – a very rare location – this case was the subject of a previous paper (25). None of the patients presented locally advanced disease or metastasis at the moment of the diagnosis.

The clinical presentation of these patients was centered on a dyspeptic syndrome (7 patients – 46.6%). The second most common clinical sing was bleeding (6 patients – 40%), one patients presenting with hematemesis (6.6%) and 5 patients presenting with melena (33.3%). Other symptoms were sub-occlusive syndrome (1 patient – 6.6%) and early satiety (2 patients – 13.3%). Other signs and symptoms were: fatigue and pallor (5 patients – 33%), significant weight loss (4 patients – 26.6%) and palpable abdominal mass (3 patients – 26.6%).

The positive diagnosis was established by contrast enhanced CT scan in 9 (60%) cases, and by endoscopy and abdominal ultrasound in the remaining 6 cases (40%). Two patients received a barium meal as a part of the diagnostic workup for gastric tumors. The 5 patients that presented with melena underwent colonoscopy to exclude colonic disease.

The type of surgical resections and the characteristics of the surgical specimens are listed in *Table 2*. In one case of ileal GIST with concomitant bile duct stones and left ovarian simple cyst, choledocholithotomy with Florcken choledoco-duodenostomy and partial cystectomy were performed.

Liver or peritoneal metastasis and lymph node involvement were absent in all cases. All the tumors had a transmural growth, without invasion of neighbouring organs.

The macroscopic inspection of the tumors revealed central necrosis and/or ulceration in 8 cases (53%). The microscopic evaluation showed that the spindle cell pattern dominated or series – 9 cases (60%), the remaining cases being described as epithelioid growth pattern. No mixt pattern was encountered. Complete resection was achieved in 14 cases (93.3%).

Immunohistochemistry, the only way to diagnose GISTs as defined today was used in all surgical specimens. All specimens were positive for CD 117 with the exception of one specimen diagnosed as GIST with the aid of CD 34 and DOG-1 (CD 117 was unavailable at the time in our Pathology department). Seven of our specimens (46%) stained positive for DOG-1 and 11 tumors (73%) stained positive for CD 34. Five specimens stained positive for all three markers.

The risk of clinical progression was evaluated according to

Table 2.

Site	Procedure	Resection, tumor size, macroscopic appearance	Microscopic appearance and IHC
Stomach (9)	Wedge resection	R0, 7/5/4.5 cm, central ulceration	Spindle cells, 4/50 HPF CD 117, CD34, DOG -1 positive
	Wedge resection	R0, 4.4/3/2 cm	Spindle cells, 1/50 HPF CD 117 positive
	Wedge resection	R0, 4.4/3.6/2.8 cm	Epithelioid cells, 2/50 HPF, CD 117, CD 34 positive
	Wedge resection	R0, 4/3.6/3.5 cm	Epithelioid cells, 4/50 HPF CD 117, CD 34 positive MALT Lymphoma Chronic atrophic gastritis with intestinal metaplasia post H. Pylori infection
	Laparoscopic wedge resection	R0, 5/4.3/3.2	Epithelioid cells, 2/50 HPF CD 117, CD 34 positive
	Partial gastrectomy	R0, 6.7/5.5/3.2 cm, central ulceration	Spindle cells, 26/50 HPF CD 117, CD 34, DOG-1 positive
	Partial gastrectomy	R0, 5.2/4.1/4 cm	Spindle cells, 2/50 HPF CD117 positive
	Partial gastrectomy	R0, 6.5/5/5 cm	Epithelioid cells, 2/50 HPF CD 117, CD 34 positive
	Upper polar gastrectomy	R1, 4.5/4/3 cm, central ulceration,	Spindle cells, 15/50 HPF CD 117 positive
Small bowel (5)	Segmental enterectomy	R0, 17/12/11 cm, central necrosis **Fig. 1* and *2*.	Spindle cells, 7/50 HPF, CD 117, CD 34, DOG-1 positive
		R0 8/5/6 cm, central necrosis	Spindle cells, 2/50 HPF DOG-1, CD 34 positive CD 117 unavailable at the time.
		R0 4/4 cm, central necrosis	Spindle cells, 3/50 HPF, CD 117, CD34 positive
		R0 11/7 cm, central necrosis	Spindle cells, 9/50 HPF CD 117, DOG-1 positive
		R0, 7/6.8/6 cm, central necrosis and ulceration	Epithelioid cells, 4/50 HPF CD117, CD 34, DOG-1 positive
Liver (1)	Atipical liver resection	R0, 5,5/5 cm	Epithelioid cells, 12/50 HPF CD 117, CD 34, DOG-1 positive AFP, CEA (polyclonal) negative

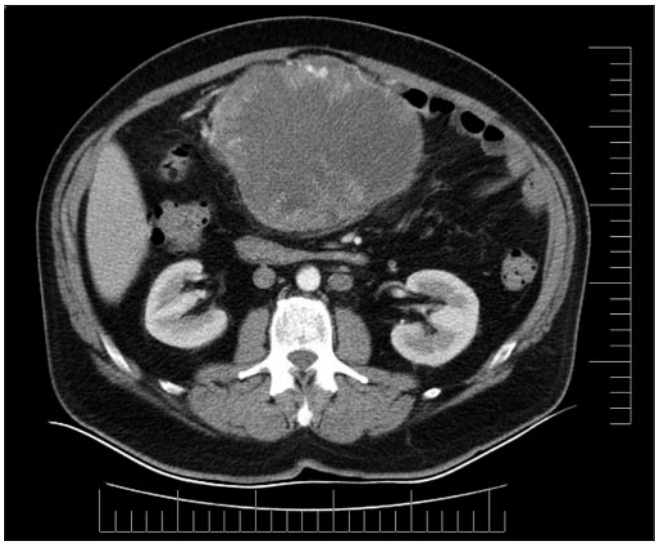

Figure 1. *Ileal GIST that presented as a sub-occlusive syndrome*

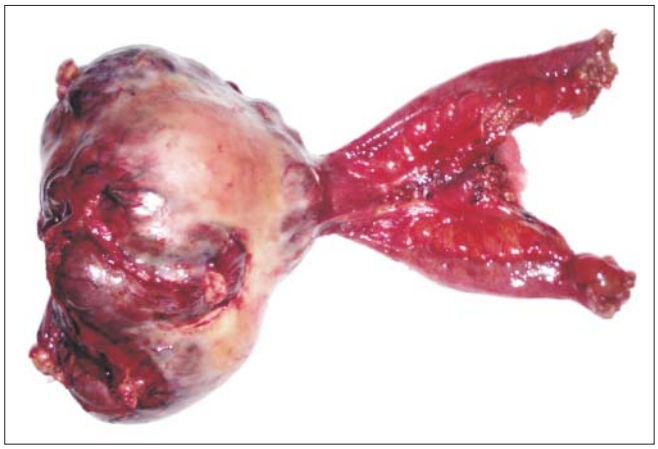

Figure 2. *Ileal GIST – surgical specimen (see Fig. 1)*

the Miettinen (17): very low risk 4 cases (26.6%), low risk 4 (26.6%) cases, moderate risk 3 cases (20%), high-risk 4 cases (26.6%).

Mean hospital stay was 8.3 days (range 4 – 18 days), with no perioperative deaths and significant events during recovery. All patients were discharged in good condition and referred to a regional Oncology center.

Discussion

Gastrointestinal stromal tumors are rare neoplasms that may arise in any part of the gastrointestinal tract – the stomach (60%) and the small bowel (30%) being the most common sites, situation encountered in our series also. Outside the gastrointestinal tract, GISTs are exceptional (< 1%), in our series – 1 case (liver) and most represent metastases of primary gastrointestinal GIST (26,27). Their origin was established in the pacemaker cells of Cajal, and immunohistochemistry (staining for CD 117 primarily but also for CD 34 and DOG-1) identifies them from the large mass of mesenchymal tumors of the gastrointestinal tract. The median age in our series (53.4 years) was smaller than the literature cited median age (60 years).

The elective treatment with curative intent for GISTs is complete surgical resection. Minimally invasive surgery is safe and effective, offering an elegant solution for approachable tumors (31). Lymphadenectomy is not necessary, since these tumors rarely metastasize to regional lymph nodes (7,28). In the case of liver metastasis, resection with safety margins if feasible is advised.

Tyrosine kinase inhibitors are can be used as neoadjuvant therapy (being effective in reducing tumor size, increasing the chance of negative margins) adjuvant therapy (reducing the chance of recurrence) and also as palliative therapy for metastatic, unresectable or reccurent disease with documented survival benefit (13).

The clinical presentation of GISTs is vague, 20% of the patients being asymptomatic and the tumors are discovered incidentally, 70% of patients are symptomatic with symptoms related to the site of the lesion and 10% of the tumors are discovered postmortem (13).

The most common symptom in our series was abdominal discomfort (dyspeptic syndrome) – 46.6% of cases, followed by bleeding – 40%. Bleeding causing melena or hematemesis and anemia is the expression of erosion of the adjacent mucosa. Sub-occlusive syndrome and a palpable abdominal mass appeared in the setting of large ileal GISTs that had a mass effect of the bowel. Early satiety (2 cases) appeared in the setting of large antral tumors and was accompanied by significant weight loss. We can state that in our series, the tumors were diagnosed in the phase of complications, no diagnosis being incidental.

The modality of choice for diagnosis is contrast enhanced computer tomography (9). The computer tomography is also used for monitoring response to therapy and recurrence control (9). In our series, the tumors were diagnosed by computer tomography in 9 cases (60%) and by upper endoscopy and abdominal ultrasound in 6 cases (40%). Other means of value for diagnosis of GISTs and especially upper gastrointestinal tumors is endoscopic ultrasound and endoscopic fine ultrasound guided needle aspiration (29).

Gastrointestinal stromal tumors are known to be associated with other malignancies, the largest group being gastrointestinal carcinomas (30). In our series, this association was found in one case (6.7%) with adjacent gastric MALT lymphoma.

Complete resection is our series was achieved in 14 cases (93.3%). Four out of our 15 cases were included in the high-risk class according to Miettinen, including the liver GIST that had large dimensions and high mitotic rate (17).

One patient with an R1 resection for a large high-risk gastric GIST was re-admitted 7 months after surgery with massive inoperable recurrence. The patient was received palliative oncologic therapy and died 2 months later.

Conclusion

Gastrointestinal stromal tumors defined as mesenchymal

tumors that stain positive at least for CD 117 are not a novelty, yet they remain a challenge for the surgeon looking for the perfect solution.

The diagnosis is made late, usually in the phase of complications. Tumor size, location and mitotic rate remain the most important prognostic factors. Risk stratification for progression should be the key factor in the management of these tumors.

Surgery (open or laparoscopic) is the primaryform of treatment and should aim to a complete radical resection without lymph node dissection unless they show evident signs of involvement. Tyrosine kinase inhibitors are new and powerful acquisitions proved to be useful both as neoadjuvant and adjuvant therapy as well as palliative therapy.

The unpredictable behavior of these tumors makeslong term oncologic surveillance necessary, independent of their initial benign or malignant characteristics.

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