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CASE REPORT

GASTROINTESTINAL STROMAL TUMOUR: PREDICTING THE RISK OF RECURRENCE OF PRIMARY TUMOURS

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Abstract. Even if they have a low incidence (0.1-3% of gastrointestinal tumours), the stromal tumours located in the digestive tract raise important issues in predicting the risk of recurrence. Their diagnosis and treatment have evolved over the last 20 years, particularly in etiopathogenic terms, due to the arsenal of laboratory investigations like imunohistochemistry and mutational analysis techniques. The main factors that determine the risk of recurrence, initially evaluated by Mietinen (2006) and subsequently clarified by Joensuu (2008, 2011) are the size, the number of mitoses, the tumour location and the intrusion capsule. The main pillars of treatment are surgery and therapy with Imatinib.
Three representative cases for the factors described and well coded as diagnosis, treatment and postoperative monitoring are presented in this article: a bulky gastric tumour and one giant gastric intestinal (resected by laparotomy) and cecal gastrointestinal stromal tumour (GIST) (rarerly concerning the location) incidentally discovered during an appendectomy, laparoscopically resolved.
The review of literature in this field combined with the clinical experience highlight the characteristics of these tumours, and, ultimately, guide the therapeutic approach in similar situations.
Keywords: GIST, recurrence risk, mitotic index, tumour intrusion.

History

The smooth muscle tumour, found in 1960, was introduced (1983) by Mazur and Clark, with the proto-oncogene mutation c-kit receptor tyrosine kinase transmembrane substrate (Hirota, 1998). GIST (gastrointestinal stromal tumour) is the most common mesenchymal tumour of the digestive system, developed from the Cajal interstitial cells [1], with the function of gastrointestinal motility pacemaker.

GIST epidemiology shows that they represent 0.1-3% of gastro intestinal neoplasms and 80% of gastrointestinal mesenchymal neoplasms during the IV-VII decades of life, with a slight predominance (54%) in men [2], the incidence of GIST [3, 4] having the following values:

- USA: 10 to 20 cases / 1,000,000
- Europe: 6-14 cases / 1,000,000
- Romania: 5 cases / 1,000,000

The GIST classification can be based on:

a) Histology [2]:
1. With spindle cells (70%) - arranged in short fascicles
2. With epithelioid cells (20%) - with nested architectural aspect
3. With mixed cells (10%) - form containing both types of cells

b) Location [5]
1. Stomach (60%)
2. Small intestine (30%)
3. Colon (<5%) - below check 1%!
4. Esophagus (<1%)
5. Rectum (<1%)
6. Extra-digestive (mesentery, omentum, retroperitoneum) <1%

Paraclinical diagnosis

- Ultrasound
- Barium
- CT / PET CT
- EDS / EDI - with ultrasound
- Ultrasound-guided fine needle puncture
- Laparoscopic Biopsy / exploratory laparotomy (assessed resectability)

Histopathologic diagnosis: spindle cell / round / polygonal / mixed.

Immunohistochemical diagnosis may reveal markers like [2]:

At these markers the protein Ki-67 is added (particularly present in tumours> 5 cm). When c-KIT is negative (5-10%) a mutational analysis is necessary, which may reveal c-KIT/PGFRA/GIST "wild" mutations.

Florin Săvulescu
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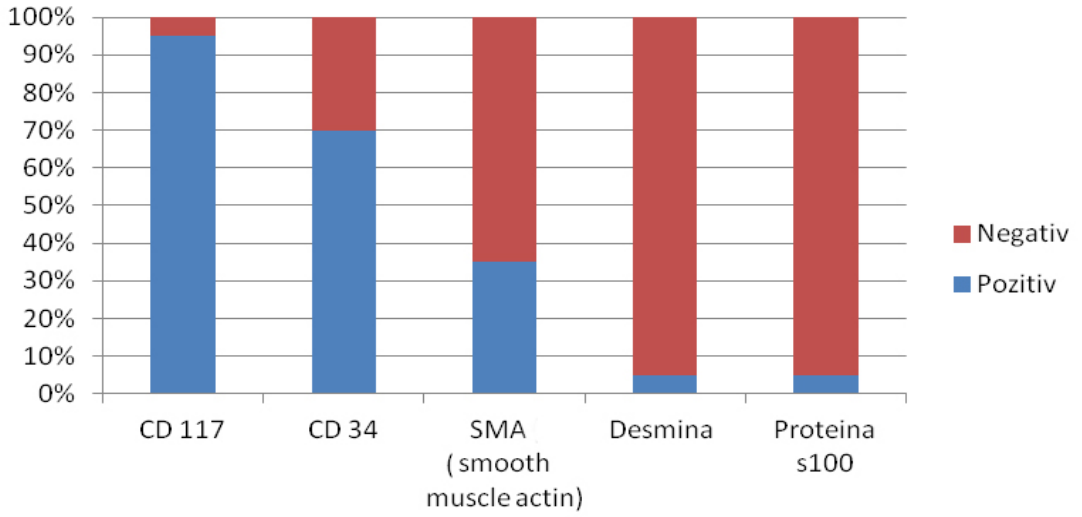

Figure 1. Immunohistochemical markers used in the diagnosis of GIST

The differential diagnosis is carried out mainly in affections as gastric ulcer disease, ectopic pancreas, adenocarcinoma, lymphoma or gastric carcinoid.

Principles of treatment

A. "Mini GIST" - submucosal nodules, incidental :

- > 2cm (histologically GIST) - resection;
- < 2cm / (histopathological non GIST) - monitoring.

B. Clinical GIST

- Macroscopic R0 resection (negative margins);
- Extended resections when the size of the tumour requires;
- Regional lymphadenectomy is not required.

C. Metastatic disease

- Initial medication (t unresectable / metastatic)
- Imatinib 400/800 mg / day, 3 years, transmembrane tyrosine kinase inhibitor or Sunitinib for primary / secondary resistant tumors at Imatinib.
- Subsequent surgery (a hepatic embolization / RF ablation for liver metastases)

Principles of surgery in primary GIST tumours [7,8]:

- R0 resection of the involved digestive segment with intact pseudocapsule.
- "Wide" resection brings no benefits
- Thorough surgical exploration to locate and to execute excision of the peritoneal tumour nodule is important.
- If the original resection is found to be R1, re-excision may be an option if it is not providing significant sequelae.

The risk of recurrence of GIST is estimated mainly by [10]:

- The size of the tumour (high risk> 10 cm)
- Mitotic rate (> 5/50 HPF)
- Location (non gastric - high risk)
- Tumour rupture (high risk)

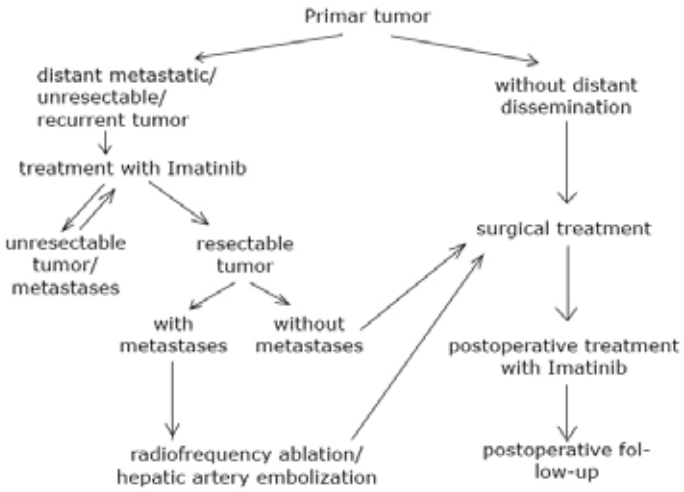

Figure 2. Scheme of treatment for primary GIST

Risk Category	Tumour size (cm)	Mitotic/50 HPFS Index	Location
Very low	<2	<5	Any
Low<10%	2-5	<5	Any
Intermediate 10-30%	2-5	>5	Gastric
	<5	6-10	Any
	5-10	<5	Gastric
High >30%	Any	Any	Tumour rupture
	>10	Any	Any
	Any	>10	Any
	>5	>5	Any
	2-5	>5	Nongastric
	5-10	<5	Nongastric

Figure 3. Classification of the recurrence risk of primary GIST (according to Joensuu 2011)

We will present three illustrative cases of primary GIST from the perspective of diagnosis, treatment and postoperative evolution, operated in the Secondary Surgery Department of the Central Military Emergency Hospital, highlighting the factors that determine the risk of recurrence, according to Joensuu (2011 criteria) :

CASE NO 1 - GIST stomach, lesser curvature

- 60 years old, M
- Clinical: palpable tumour, heartburn
- Location: small curvature
- Macroscopic: exofitic tumour, diameter of 20 cm
- Adjacent Invasion: omentum
- Metastases: NO
- Immunohistochemistry: c-KIT positive
- Mitosis: 10/50
- HIGH recurrence risk > 30%

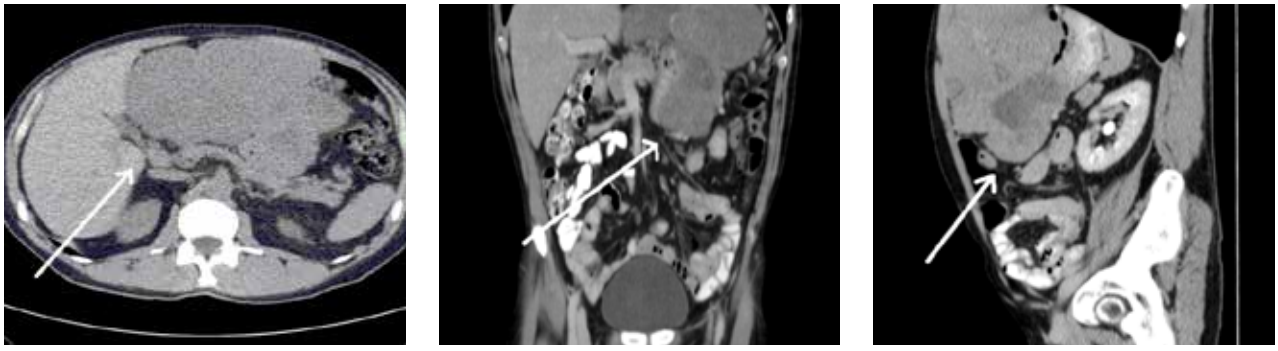

Figure 4. Gastric GIST, CT scan, a cross-sectional front sagittal section

Figure 5. Gastric GIST, intraoperative and resection piece images

CASE 2 - bowel GIST

- 60 years old, M
- Clinical: palpable tumour, abdominal pain.
- Location: small intestine at 1.2 m from the Treitz angle
- Macroscopic: encapsulated tumour, 25 cm diameter
- Adjacent Invasion: omentum
- Metastases: NO
- Immunohistochemistry: c-KIT positive / vimentin + / actin + / Ki67
- Mitosis: 10/50
- HIGH recurrence risk, > 30%

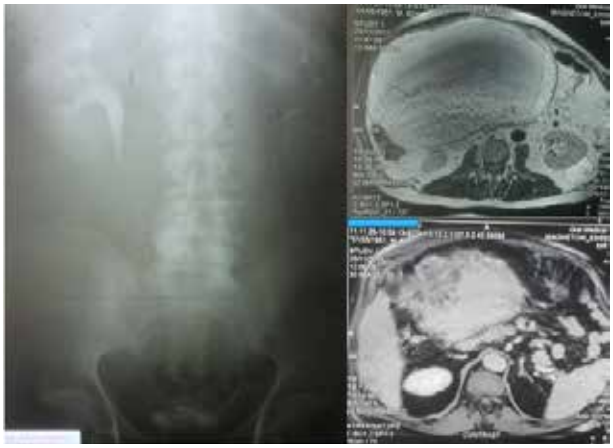

Figure 6. Small intestine GIST: Urography Exam, MR and CT

Figure 7. Small intestine GIST - c-kit mutational analysis in exon 11

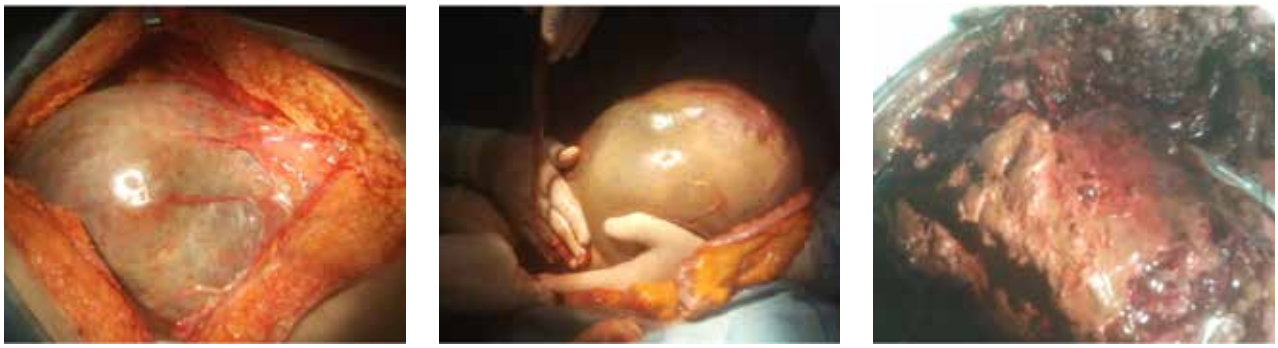

Figure 8. Small intestine GIST - Intraoperative and resection piece view

CASE 3 – CEC GIST

- 34 years old, F
- Clinical: colicky pain in the FID
- Location of lesion: cec - the medial face
- Macroscopic: encapsulated tumour, 4 cm in diameter
- Adjacent Invasion: NO
- Metastases: NO
- Immunohistochemistry: c-kit positive (!)
- Mitosis: 2/50
- LOW recurrence risk <10%

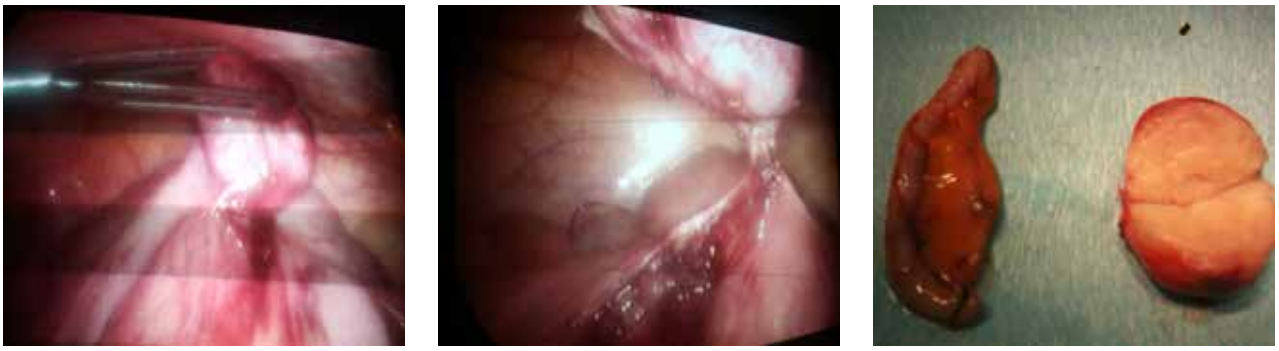

Figure 9. Cecal GIST intraoperatively diagnosed: Laparoscopic appendectomie and tumorectomie

Postoperatively, all 3 cases received imatinib 400 mg, patients were periodically evaluated, clinical and laboratory examinations, none showed signs of relapse at 3, 2 and 2.5 years after surgery.

Conclusions

GIST is currently an underdiagnosed pathology, given that within the EU incidence in relation with the Romanian population, it should result in 300 cases discovered annually, while in Romania the actual incidence is 100 cases. This highlights the importance of the quintet: gastroenterologist – surgeon – radiologist – pathologist – oncologist.

The characteristics of gastrointestinal tumours are: relatively low incidence, difficulty regarding preoperative diagnostic and variable malignant potential.

Patient prognosis depends on rapid diagnosis and intervention, the presence of possible complications and the degree of malignancy.

Surgery is the main curative treatment in the localized disease and resectable, followed by treatment with Imatinib.

In the metastatic disease, Imatinib plays a neoadjuvant role, followed by elective surgery.

The risk of recurrence of GIST depends mainly on: the tumour size, the mitotic rate, the tumour intrusion and localization.

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