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Management of Gastrointestinal Stromal Tumors: Experience of a University Hospital

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Authors' contributions

This work was carried out in collaboration among all authors. Authors EA and AM designed the study, performed the statistical analysis, wrote the protocol and wrote the first draft of the manuscript, managed the analyses of the study and managed the literature. All authors read and approved the final manuscript.

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Case Study

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ABSTRACT

Gastrointestinal stromal tumors or GISTs are rare tumors: 1 to 3% of malignant tumors gastrointestinal. 65% of these tumors sit in the stomach, 25% in the small bowel, 5-10% in the colon-rectum...
They occur secondary to activating mutations of the KIT or PDGFRA receptors. In 85% of cases, and are diagnosed at a localized stage in about 85% of cases. The spontaneous recurrence rate for patients who have undergone surgery and have a complete resection is approximately 40% at 10 years.
In this article we present a case of a gregarious stromal tumor whose age of occurrence was early and recurrence after complete surgical resection and targeted therapy was rapid and aggressive.
Also we discuss in the light of the literature, the results, surgical treatment, targeted therapy, histological findings and prognostic factors on which the risk of recurrence depends.

Keywords: Gastrointestinal stromal tumors (GIST); pathogenic factors; prognosis; early recurrence.

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1. INTRODUCTION

Gastrointestinal stromal tumours (GISTs) are rare, usually sporadic, conjunctive tumors, frequently located in the stomach or bowel. However, they are the most frequent sarcomas [1,2]. They are derived from Cajal cells or one of their precursors and typically express the KIT+ (95% of cases) and DOG-1+ (95% of cases) phenotype. An oncogenic mutation of the KIT or platelet derived growth factor receptor alpha (PDGFRA) genes encoding tyrosine kinase-type receptors is found in approximately 85% of adult GISTs [2].

These mutations are the essential pathogenic factor causing activation of the KIT or PDGFRA proteins. The discovery of the efficacy of tyrosine kinase receptor blockers (TKIs), first imatinib, then sunitinib and regorafenib, has changed the prognosis for GISTs.

65% of these tumors are located in the stomach, 25% in the small bowel, 5 to 10% in the colon and rectum....

Their incidence is estimated at about 15 cases/ 1000000 inhabitants per year. The malignancy potential on which the prognosis and the risk of recurrence of these tumors depends is correlated to the location, the size of the tumor and the mitotic index.

We present a case of a gregarious stromal tumor in the age of occurrence being early and the recurrence after total surgical resection and targeted therapy was rapid and aggressive.

We discuss in light of the literature, the results, surgical treatment, targeted therapy, histological findings, as well as prognostic factors on which the risk of recurrence depends ...).

2. CASE PRESENTATION

Mr A M aged 34 years, without any notable pathological antecedent consults for hypogastric pain evolving 20 days before his admission, without transit disorder, without externalized digestive haemorrhage, without urinary signs, evolving in a context of Alteration of the General State.

The Clinical Examination finds a hypogastric mass which extends to the Fig of 10 cm, hard and painful, mobile to both superficial and deep planes, Examination of the ganglionic areas are free. The rest of the clinical examination was without particularity.

CT scan A-P: Presence at the hypogastric level, above the bladder of a tissue formation measuring 65*80*105 mm, this formation is in intimate contact with the recto-sigmoid digestive structures. No locoregional or remote extension.

Recto-sigmoidoscopy: the endoscopic exploration of the different segments is without particularity.

The patient benefited from resection of a bowel mass 2 m from the ADJ with terminal anastomosis , on exploration: presence of a 20 cm solidocystic mass located 2 m from the ADJ, non-stenosing in contact with the bladder without invading it. No carcinoid nodules or liver metastasis with moderate abundance of ascites.

In Anapath malignant fusocellular tumor proliferation measuring 13 cm below the mucous membrane extended to the ulcerated serosa evoking first a high-risk gastrointestinal stromal tumor, the mitotic count is very high 28 mitose/ 10CFE, presence of vascular embolus, healthy longitudinal limits. Immuno-histochemical study: presence of the C-kit gene mutation which confers sensitibity to imatinib.

The postoperative follow-up was simple, and the patient was followed up in oncology and put on imatinib 400 mg/d.

The evolution was marked by the appearance 2 months after surgery of diffuse abdominal pain, associated with the progressive onset of a sub-occlusive syndrome, with bilious vomiting,

2.1 Clinical Examination

Conscious patient 15/15 hemodynamicaly and respiratory stability, pale with discolored conjunctiva, altered facial appearance. Dehydration folds. FC=96 bpm TA=10/6 FR=24 cpm T=37 BMI=16.4 kg/m2.

Abdominal Examination: Medial laparotomy incision, abdomen very distended and tympanic with the presence of a large abdomino-pelvic mass of 25 cm in diameter, firm and painful, fixed in the deep plane. Rectal touch: presence of a mass at the CDS of douglas. Examination of the lymph node areas: free. The the rest of the clinical examination was unremarkable.

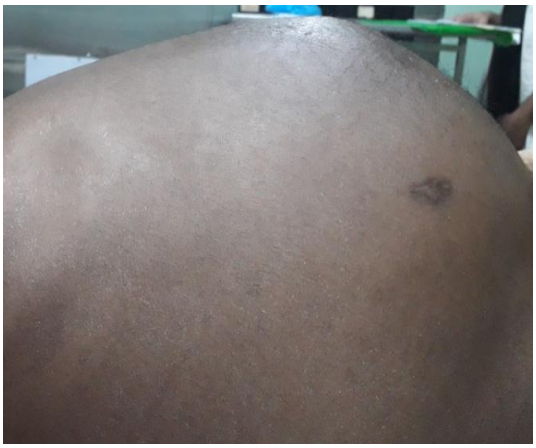

Fig. 1. Giant abdomen distension

2.2 CT A-P

Presence of two abdomino-pelvic masses of solid-cystic appearance encapsulated with polylobate contours, measuring 25x21x19 cm originates in the small bowel, with hydro-aeric distension of the bowel.

The second mass is lateralized on the right mesuring 9*8*6.5 cm.

These masses compress the bladder and the two ureters with bilateral moderate UHN.

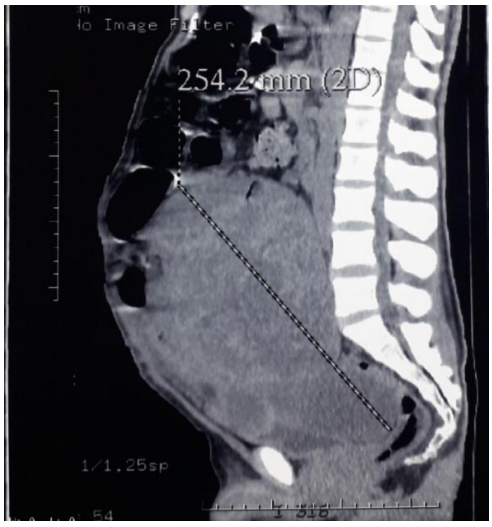

Fig. 2. Large abdomino-pelvic mass measuring 25x21x19 cm

The patient underwent an ileo-caecal resection with 1 m of bowel and two abdomino-pelvic masses with Ileo-colostomy.

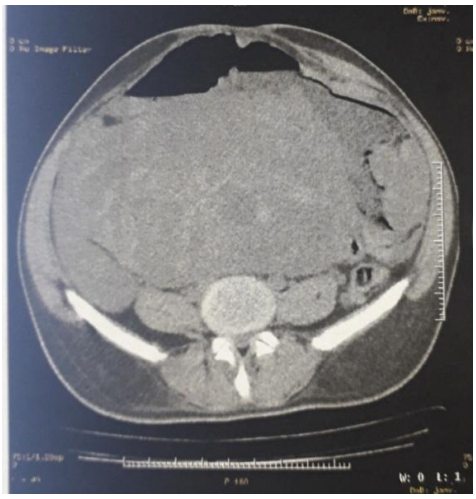

Fig. 3. Large abdomino-pelvic mass measuring 25x21x19 cm

In exploration: presence of a voluminous abdomino-pelvic mass mesuring 24 cm causing a grelic distension of 5 cm, contact with the bladder and the anterior face of the rectum. Presence of a second mass mesuring 10 cm at the expense of the last bowel.

2.3 Anapath

Mixed tumour proliferation with fusiform cells and remodeled epitheloid measuring 22 cm compatible with the already diagnosed GIST of high risk of recurrence according to JOENSU's criteria. Limit of resection free, no lymph node metastasis: 0N+/ 9N.

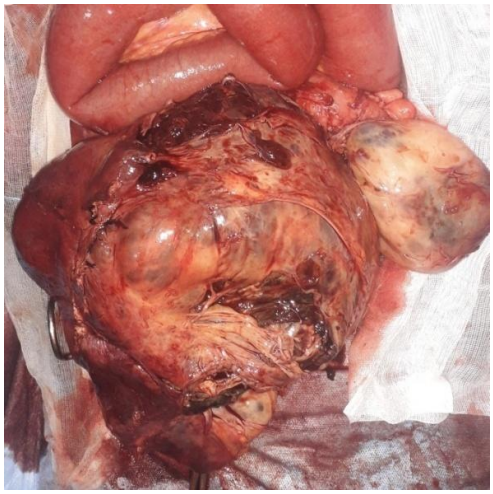

Fig. 4. Intra-operative showing a giant and aggressive reccurence GIST

3. DISCUSSION

Gastrointestinal stromal tumors or GISTs are rare tumors: 1 to 3% of gastrointestinal malignancies. They are cell proliferations, usually fusiform, sometimes epitheloid, rarely pleiomorphic expressing the C-kit in 90 to 95% of cases [3].

Stromal tumors are rare before the age of 40 and exceptional in children, with a mean age of discovery between 55 and 65 years [4], in our patient the age of appearance of GIST was early (34 years) compared to what is reported in the literature.

In about 85% of cases GIST is diagnosed at the localized stage. The spontaneous recurrence rate for patients who have undergone surgery and have a complete resection is about 40% at 10 years of age. Recurrences are mainly hepatic or peritoneal, sometimes locoregional in gastric or rectal GIST. Most occur within 5 years, especially in the first 2-3 years. Later recurrences are rare.

In our patient, the recurrence is locoregional, voluminous 25 cm very early (2 months after complete surgical resection).

Estimating the risk of recurrence is essential for the indication or not of an adjuvant treatment, which is now a standard in some cases, and for adapting surveillance [5,6].

For localized GISTs, the risk of recurrence is currently assessed according to the primary localization, size and mitotic index (the most important parameter) evaluated over 5 mm2. Depending on these parameters, the risk of recurrence may be almost zero, or exceed 70% [7].

Our patient had an intestinal GIST, the tumor size was 13 cm, and the mitotic index was very high 28 mitose/ 10 CFE. Other parameters are also important, such as tumor rupture in the abdominal cavity, spontaneous or preoperative, or a high risk of peritoneal recurrence [8]. The combination of these prognostic markers has made it possible to define groups of patients with different levels of risk of recurrence.

A few classifications for estimating the risk of recurrence of GIST after R0 resection have been proposed. They are all valid, and all have limitations. They are based on retrospective historical series before the advent of adjuvant therapy and do not incorporate molecular data.

Miettinen's AFIP and Joensuu's modified NIH classifications (Tables 1 and 2) are the most widely used in Europe [7,8]. In our patient, the risk of recurrence, according to both AFIP and NIH classifications was high. It was estimated at 90% according to the AFIP classification.

Genotype is a complementary tool for assessing recidivism risk [5,6]. These data are gradually beginning to be added to the histological criteria, which are still predominant for estimating the risk of recurrence [9]. The relationship between genotype and recurrence risk is complex to analyze for several reasons. On the one hand, because there is a wide variety of possible mutations at the level of exon 11 of KIT. However, ten mutations represent more than 50% of all mutations allowing certain genotype/prognosis correlations.

On the other hand, in addition to its prognostic value, the mutation is also predictive of response to imatinib treatment. Thus, mutations in KIT exon 11 are the most sensitive to imatinib, while the PDGFRA D842V mutation is generally resistant.

In practice, GISTs with KIT mutation have a higher risk of recurrence than those with PDGFRA mutation, while GISTs without KIT/PDGFRA mutation have an intermediate risk between these two groups. Among exon 11 KIT mutations, deletions have a higher risk of recurrence than substitutions and duplications (rarer) have a better prognosis [5,6,9].

Remember that in our patient we note the presence of the mutation of the C-kit gene which confers a sensibility to imatinib and our patient was treated with imatinib 400 mg/day.

Estimating the risk of disease recurrence or death in localized GISTs resected in groups defined by tumour size, mitotic index and tumour site.

(AFIP: Armed Forces Institute of Pathology). (According to Miettinen [10]. Figs are based on long-term follow-up studies of 1055 gastric GISTs, 629 jejuno-ileal GISTs, 144 Duodenal GIST and 111 Rectal GISTs and finally perforation, which is associated with a high risk of recurrence, should be added.

Table 1. Evaluation of mitotic index from GIST

Tumor maximal diameter (cm)	Mitotic index **	GIST gastric	GIST jéjuno-iléal	GIST duodénal	GIST rectal
≤2	≤5	0	0	0	0
>2 -5	≤5	1,9 % (très faible)	4,3 % (faible)	8,3 % (faible)	8,5 % (faible)
>5 -10	≤5	3,6 % (faible)	24 % (intermédiaire)	-*	-*
>10	≤5	12 % (intermédiaire)	52 % (élevé)	34 % (élevé)	57 % (élevé)
≤2	>5	0	50 % (élevé)	-*	54 % (élevé)
>2 -5	>5	16 % (intermédiaire)	73 % (élevé)	50 % (élevé)	52 % (élevé)
>5 -10	>5	55 % (élevé)	85 % (élevé)	-*	-*
>10	>5	86 % (élevé)	90 % (élevé)	86 % (élevé)	71 % (élevé)

** insufficient number of patients for estimation*

*** the mitotic index is evaluated by Miettinen on a global surface of 5 mm2, estimation of the 50 classical high magnification fields in order to limit the variability according to the microscopes (this corresponds indeed to only 20-25 high magnification fields on recent microscopes)*

Table 2. Estimation of the risk of recurrence in localized GIST resected

Risk of reccurence	size	Mitotic index	Localisation
Très faible	≤ 2 cm	≤5	Indifférent
Faible	>2 – 5 cm	≤5	Indifférent
Intermédiaire	≤5 cm	6-10	Gastric
	>5 – 10 cm	≤5	Gastric
Elevé	Indifférente	Indifférent	Rupture tumoral
	> 10 cm	Indifférent	Indifférent
	Indifférente	> 10	Indifférent
	> 5 cm	> 5	Indifférent
	≤ 5 cm	> 5	Non gastric
	>5 – 10 cm	≤5	Non gastric

Estimation of the risk of recurrence in localized GIST resected in the classification of Joensuu derived from that of the NIH. It aims in particular to better separate the GISTs at risk intermediate and high, and incorporates the pejorative character of a perforation [4].

4. CONCLUSION

GISTs remain rare, mostly sporadic tumours in adults, mainly in the stomach and small intestine, with a histological diagnosis. They occur secondary to activating mutations of the KIT or PDGFRA receptors in 85% of cases, and are diagnosed at a localized stage in about 85% of cases. Surgery at the outset is the potentially curative treatment for localized GIST. Histo-prognostic classifications taking into account tumour location, tumour diameter, mitotic index and whether or not the tumour is punctured (Miettinen or Joensuu) make it possible to classify GISTs according to their risk of relapse and to pose a risk to the patient.

The indication has an adjunctive treatment with imatinib, the standard being 3 years, but the optimal duration has yet to be determined. Imatinib, a tyrosine kinase inhibitor targeting KIT and PDGFRA, has completely changed the prognosis of these tumors. It is the only first-line treatment for metastatic or locally advanced GIST.

CONSENT AND ETHICAL APPROVAL

As per international standard or university standard guideline participant consent and ethical approval has been collected and preserved by the authors.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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