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Gastrointestinal Stromal Tumors "GIST": Status and News through Our Experience on 64 Cases and Review of Literature

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Abstract **Original Research Article**

Gastrointestinal Stromal Tumors "GIST" are a very rare form of digestive tract cancers belonging to the family of sarcomas. The aim of this study is to establish the epidemiological and evolutionary profile as well as the diagnostic and therapeutic difficulties of this malignant pathology managed in a developing country. A retrospective study spread over 13 years from January 2006 to December 2018, was conducted at the Visceral Surgery Service of university hospital Mohammed VI in Marrakech (Morocco) have collated 64 cases of gastrointestinal stromal tumors. The average age of our patients was 53 years. The average progression time was 7.5 months. The Biopsy confirmed the diagnosis in 17 cases and surgery in 47 cases. The main histological form was fusiform (60.94%). GIST in our series had an average tumor size of 8.2 cm with a positive C-Kit in all cases. The risk of progression was identified in 56 cases, 10 of which were high risk. Surgery was the main treatment for patients in our study. After a mean fellow of 31 months, 43 of the evaluable patients in our series are in full remission maintained, 10 cases have local and/or metastatic recurrence and one death. Although the recommendations are published for the treatment of these tumors, these still raise many problems both diagnostic and therapeutic in our context.

Keywords: Gastrointestinal stromal tumors, GIST, epidemiology, diagnosis, treatment.

INTRODUCTION

Gastrointestinal stromal tumors “GIST” are mesenchymal tumors that most often develop from Cajal cells in the lining of the digestive tract and are exceptionally extradigestive. Although GIST is the most common sarcoma of the digestive tract, it accounts for only 0.2% of digestive malignant tumors, with an estimated incidence in Sweden and France of about 12-15/1,000,000 inhabitants per year [1, 2]. They are characterised by overexposure of C-kit in immunohistochemistry and by activating mutations of tyrosine kinase receptors. These tumors have a known malignancy potential, and their prognosis is correlated with location, tumor size and mitotic index. Surgery is the reference treatment for localized forms. Targeted therapies, such as Imatinib and then Sunitinib, have transformed the management and prognosis of advanced and metastatic forms.

METHODS

This is a 13-year retrospective study carried out within the visceral surgery department of university hospital Mohammed VI in Marrakech (Morocco). A series of 64 consecutive cases of gastrointestinal stromal tumors collided in service between January 2006 and December 2018 was studied. Data were collected from medical records, operational and anatomopathological reports. Included in the epidemiological study were all patients referred to the service for histologically confirmed gastrointestinal stromal tumor management. Patients who were lost after the first consultation were excluded from the analysis of therapeutic and developmental outcomes. Due to the small numbers, the statistics produced on this series were only descriptive.

RESULTS

Description of the population

The average age of our patients was 53 years (27-80 years) with a higher frequency for the 40-60 years (65.6%). A discrete male predominance was noted with a gender ratio of 1.46. The most common location was gastric (59.37%), followed by the small intestine (26.25%) then rectal (7.81%) and mesenteric (6.25%)(Figure 1). The average development time was 7.5 months (0-72 months). In most cases (95.31%), the tumor was symptomatic and the main symptom was pain (Figure 2). Biopsy confirmed diagnosis in 21

patients on endoscopy. Surgery was the means of diagnostic confirmation in 43 patients. The histological study showed a predominance of the fusiform form (60.94%), while the epitheloid form and the mixed form were found respectively 29.68% and 9.37% of cases. The average tumor size was 8.2 cm (2-15 cm). The mitotic field index (High Power Field: HPF) was only reported in 22 patients with HPF > 5/50 in 14 cases.

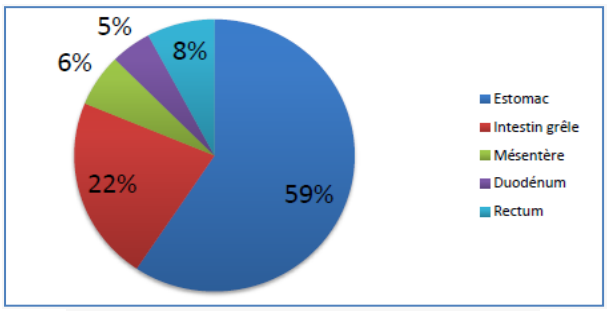

Fig-1: Distribution of GIST by location in our series

The C-kit, performed in all patients of our series, was positive in all cases. Molecular biology has not been realized in our patients. The evolutionary risk could be established in 56 cases. At the end of the radiological and histological assessment, the diagnosis of localized GIST was retained in 53 cases, locally advanced in 7 cases and metastatic in 4 cases.

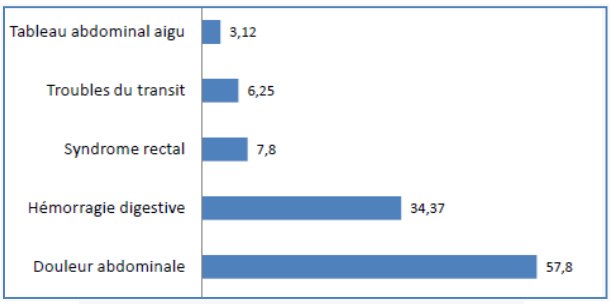

Fig-2: Clinical signs revealing GIST in our series

Therapeutic management

Imatinib was initially indicated at 400 mg/J for the 4 metastatic patients and in a patient with locally advanced rectal GIST. Surgery was the main treatment of patients in our series, performed immediately in 60 patients and after neoadjuvant treatment with Imatinib following a partial response, in two other cases. Surgery was R0 in 42 cases, R1 in 13 cases and R2 in 5 cases. In adjuvant surgery, the indication of Imatinib was given in multidisciplinary consultation meeting, for 12 patients, only 7 of them received it. For an average duration of 12 months (3-21 months). The progression in these patients was marked by the maintenance of complete remission in 43 patients, partial remission in 3 cases, and local and/or metastatic recurrence in 5 patients. There were 2 cases with tumor progression with one death.

The monitoring time was once a month for the first three months after surgery, then once every six months. The average decline in our series was 57 months (with extremes ranging from 5 months to 8 years).

DISCUSSION

Gastrointestinal stromal tumors or GIST are rare tumours: 1 to 3% of gastrointestinal malignant tumors. These are proliferations of cells, most often fusiform, sometimes epithelioid, rarely pleiomorphs emerging in the muscular digestive tract and expressing CD117 or C-kit in 90-95% of cases, NSE in 85-90% and CD44 in 60-80% [3]. The suggestion that C-kit positivity is required for GIST diagnosis is therefore questioned [4]. In fact, there are rare exceptions, representing a maximum of 5% of cases, where the C-kit protein is not detectable by immunohistochemistry [5, 6]. These tumors may be referred to as negative GIST C-kit or rather "GIST-compatible fusiform cell or epithelioid stromal tumors". GIST tumorogenesis involves two receptors: C-Kit and PDGFR. Mutations of these receptors are heterozygous type gain of function [7, 8]. The gene coding for the C-kit protein can be the site of mutations in 85% of cases and which are preferentially membrane juxta (Exon11), may also concern the extracellular region of the protein (Exon 9) rarely from other parts of the protein, as for the PDGRF gene its mutation is less frequent (10-15%). In our series, the impact of c-kit negative GIST is consistent with the literature. As for the mutational profile, a comparison cannot be made since the molecular study was not carried out in our patients. Stromal tumors are rare before 40 years and exceptional in children with an average age of discovery between 55 and 65 years [9]. There is no clear predominance of sex, only some studies show a discrete predominance of males with a sex ratio close to 1.5 [10-12]. These data are consistent with the results of our series where the average age is 53 years and the sex ratio Male/Female 1.46.

The GIST can be found throughout the digestive tract, the topographical distribution of GIST in our series is similar to that reported in the literature. In fact, gastric GIST represent the first location (59.37% versus 60-70%), the small intestine is the second location both in our series and in the literature with an almost similar frequency (26.25% versus 20-30%). The multifocality of GIST remains exceptional; no case of our series has been noted. The extra-digestive forms, are rare represent less than 5%; they are mainly mesenteric, intra-hepatic [13] or intra-pancreatic localisations have been described [14, 15]. In our series the only extradigestive location is mesenteric with a discreetly higher frequency (6.25%). Stromal tumors are long asymptomatic, making their discovery frequent by chance. Off in our series, most cases the tumor was symptomatic. This could be justified by the delay in the

development of the symptomatology before the first consultation which is on average 7.5 months (0-72 months). The discovery at a metastatic stage was not the same in our series as that reported in the literature with respectively 6.25% and 15-25% of cases [16]. The particularity of our series can be explained by a recruitment bias. In fact, patients referred to our structure generally have resectable GIST. In our series, pain was the main symptom (57.8%) followed by digestive hemorrhages in 34.37% of cases. However, the review of the literature finds that digestive hemorrhages are most often indicative of GIST (48% of cases) as to pain its frequency does not exceed 36% of cases [17]. Other functional signs are closely related to the tumor site.

Any GIST is considered potentially malignant [18] and should therefore theoretically be respected. Lymphatic treatment in GIST is not carried out systematically [19, 20] because, as with other sarcomas, GIST are not very lymphophilic: the rate of lymph node invasion is usually less than 10% and the risk of lymph node recurrence is less than 5%. Unlike other sarcomas, there is no consensus as to whether a preoperative diagnosis by puncture-biopsy (endoscopic, percutaneous or operative) is necessary in the case of a resectable tumor. The surgical treatment of a gastrointestinal stromal tumor must be macroscopically complete, free of tumor invasions and with healthy margins, while favouring functional exeresis. Indeed, the extraction banks must be free of tumor infiltration [19-21], but there is no consensus on the necessary safety distance between the edge of the tumor and the surgical section. However, a margin of 1 to 2 cm is generally considered sufficient. When the lesion is resectable, neoadjuvant treatment with Imatinib is not indicated [19], on the other hand, Imatinib may be indicated after multidisciplinary consultation when it is considered that it can modify the operative gesture by simplifying the surgery or by allowing a less mutilating resection (sphincterian preservation for the rectum for example). In our series, the surgery was performed in 60 three patients, quality (R0) in 42 patients or 65.6% whereas it was 40% in the Dematteo series [22]. It should be noted that two cases in this group (R0) were considered initially unresectable, and which responded favourably (partial response of 25 and 60%) to the neoadjuvant Imatinib treatment received for 8 and 5 months respectively. After an average decrease of 31 months (2-106 months), the evolution in the patient group (n=55) with complete resection (R0+R1) was marked by the maintenance of complete clinical and radiological remission in (58.6% consistent with literature data at a median time of 2 years (40-60%) [23]. to compensate for the frequency of recurrence, adjuvant treatment is required. Outside, the efficiency of systemic chemotherapy in stromal tumors is low, with response rates of 0-10%. This chemoresistance could be explained on the one hand, by the strong expression of proteins of resistance to anticancer (Glycoproteinep and protein of multi-drug-1 resistance), on the other hand via the anti-apoptotic signal emitted following the activation of the C-Kit [24]. Therefore, the selective inhibitory action of the c-kit protein possessed by Imatinib and the positive results of the ACOSOG Z9001 study justify its use by adjuvant in GIST c-kit positive to high recurrent pontential. In order to determine this risk of recurrence, the National Institute of Health (NIH) proposed a prognostic classification in 2002 based on two histological criteria: the size of the tumor in its largest diameter and the mitotic index for 50 high-magnification fields [5]. In 2006, Miettinen demonstrated by drawing on a large series from the Armed Forced Institute of Pathology (AFIP) that the tumor site, for the same size and mitotic index, is also a prognosis factor. Thus hail GIST would have a greater pontentiel of recurrence than gastric GIST [25, 26]. In our series, the risk of recurrence, according to the AFIP classification, was high in 10 patients and moderate in 34 cases. In 12 cases, the risk was low. For the remaining 8 cases, it was not possible to conclude a specific risk of recurrence because the mitotic index is not available.

In our series, Imatinib was indicated by adjuvant to surgery in 12 patients, only 7 of them received it, lack of financial means. The evolution of this group of patients (n=7), was marked by the maintenance of complete remission in the 4 cases, a partial response estimated at 65% was observed in one case. While the evolution was unfavourable in the other cases (n=2), with a tumor progression in one patient and a local and metastatic recurrence in the other after a delay of 8 and 17 months. This non-response to Imatinib could be related to resistance, without being able to rule out the possibility of a problem of compliance. In fact, resistance to Imatinib can result in a progression either at the beginning of the treatment (6 months) called "primary resistance" of the order of 10 to 15%, or later (>1 year) called "secondary resistance" in about 15% [23]. This clinical evolution is mainly related to the mutational profile of the tumor. Thus mutational research, in addition to its diagnostic role, has a prognostic and predictive interest in the response to anti- C-kit therapies. In fact, the response rates are 83.5% for exon11 versus 47.8% for exon 9 [27] and progression-free survival at 24 months is 69% for exon 11 versus 14% for exon 9 [28]. Therefore, the recommended dose of imatinib if mutation on exon 9 is immediately 800 mg/d [29]. Admittedly, the tolerance of Imatinib is dose dependent, nevertheless the majority of side effects are often of moderate intensity and usually regress during treatment. The three most common side effects reported in the literature are edema, asthenia and digestive disorders [30, 31]. Similarly in our patients, the tolerance was overall good with 16.7% of side effects, requiring the definitive cessation of Imatinib only in one case. The standard treatment, of patients developing primary or secondary resistance as well as those exhibiting intolerance to

Imatinib which proves rebellious to symptomatic treatment, is Sunitinib. The latter is an inhibitor of both PDGFB and VEGF receptors. It therefore possesses a powerful antiangiogenic activity in addition to its direct anti-tumour activity.Its effectiveness was demonstrated by a multicentric phase III study published in 2006, with a gain in survival without progression in the Sunitinib arm (6.4 months vs 1.5 months; p 0.0001) [32, 33]. Other targeted therapies such as Nilotinib, Sorafenib and Mastinib are being tested [34, 35].

CONCLUSION

The spectacular advances in molecular biology, will certainly lead in the near future to a personalized and definitive treatment of gastrointestinal stomach tumors. In the meantime, in our context, the socio-economic level is a real barrier for the clinician limiting the quality of therapeutic management. However, significant efforts are underway to improve access to targeted therapies for low-income patients.

Current state of knowledge on the subject

• Rare mesenchymal tumor of the potentially curable digestive tract (Complete remission 60-70%);
• Rare before age 40, ckit positive >95%;
• Most common gastric location.

Contribution of our study to knowledge

• Chance discovery is often found in literature outside it is rare in our series;
• Frequency of symptom master pain in our series while digestive hemorragy is the main symptomatology reported in the literature.

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