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Research Article

Management of Stromal Tumors of The Small Intestine

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Summary

Small intestine stromal tumors represent 20 to 30% of all GISTs, they are the most common mesenchymal tumors of the digestive tract. This work is a retrospective study of a series of six cases of small intestine GIST, treated and followed in the service of visceral surgery at the Moulay Ismail Military Hospital in Meknes-Morocco. Small intestine stromal tumors are a delicate and rare entity given the variable clinic, abdominal CT with a thoracic passage is the reference examination for diagnostic orientation. The diagnosis of certainty is mainly based on anatomopathological and immunohistochemical study; R0 surgical resection is the only curative treatment.

Introduction

Gastrointestinal stromal tumors commonly known by their acronym GIST (Gastro-Intestinal Stromal Tumors) are rare tumors of the digestive tract. Twenty years ago, the majority of mesenchymal tumors of the digestive tract were considered smooth muscle tumors (leiomyomas, leiomyosarcomas, etc.) [1].

In 1983, Mazur and Clark introduced the term gastrointestinal stromal tumor (GIST) to describe a distinctive type of non-smooth muscle mesenchymal tumors. [2] Since then, the in-depth study carried out on mesenchymal tumors of the digestive tract has shown that the vast majority of these tumors are GISTs with a specific etiogenesis unrelated to the gastrointestinal smooth musculature at the expense of which, it is true, they develop. [3] The histological characteristics of GISTs may explain this long confusion, but it is currently clearly demonstrated that GISTs develop due to the occurrence of specific oncogene mutations from pacemaker cells of the digestive tract and have a specific immunohistochemical profile. Although low, the incidence of GISTs has tended to increase in recent years [4] and the progress made in their treatment has made it a tumor pathology of great interest. [1,5] The majority of GISTs develop in the stomach (~60%), then the small intestine (~30%) and more rarely in other segments of the digestive tract. [6,7,8] The treatment of GIST thus combining a surgical approach, a molecular treatment and a new technology such as liver radiofrequency makes it a model of multidisciplinary care which will probably spread to other cancers in the future close [5-7].

Using the observation of patients with stromal tumors of the small intestine in the visceral surgery department of the Moulay Ismail Meknes Military Hospital, we will specify the different clinical, paraclinical, anatomo-pathological, prognostic and current therapies specific to GISTs of the small intestine. We will also analyze the main complications and the impact they may have on the course of the disease and the management of the patient.

Materials And Methods

Our work is a retrospective study concerning 6 cases of small bowel stromal tumors collected in the visceral surgery department of the Moulay Ismail Meknes Military Hospital, over a period of 6 years (January 2014-December 2019).

Results

Clinic

- Abdominal pain is the main symptom when these tumors are discovered. It was present in 4 of our patients. The hemorrhagic syndrome was observed in the form of melena, inaugural in 2 patients. The deterioration of the general state was noted in 2 patients. Only one patient consulted for the appearance of an abdominal mass.
- The clinical examination revealed during abdominal palpation: An abdominal mass in 4 patients, mucocutaneous pallor was observed in 2 patients, HSMG was noted in a single patient, tarry and black stools in a single patient rectal examination patient.

Diagnostic

All patients benefited from a biological assessment which objectified anemia in 4 patients, 2 cases related to melena. Abdominal ultrasound was performed in a patient showing digestive thickening. All cases in our series benefited from abdominal CT. It made it possible to specify: The location of tumors, The measurement of tumor masses, the search for secondary locations or tumor recurrence, the evaluation of complications.

Pathological Anatomy

The macroscopic appearance of the lesions was detected using abdominal CT in all patients in our series. The average size of the tumor was 6 cm with extremes ranging from 3 cm to 10 cm.

The microscopic study was carried out from the surgical specimens in 5 cases of our series, one patient benefited from a radio-guided percutaneous biopsy; Spindle cells were found in 5 patients, epithelioid cells were not found in any patient in our series.

The limits of the resection were healthy in the 5 operated patients.

5 patients in our series benefited from an immunohistochemical study: CD 117 was positive in 5 patients, CD 34 was positive in 3 patients and negative in 2 patients, DOG 1 was performed in 5 patients and came back positive, the PS100 was performed in 1 patient, came back negative.

Treatment

- 5 patients in our series underwent surgical treatment: all operated patients underwent R0 resection and were all operated by midline laparotomy. The postoperative course was simple in the 5 operated patients. Morbidity related to surgery was found in a single patient: Anemia requiring a transfusion. Mortality was nil.
- 4 patients had received Imatinib as an adjuvant after surgical resection of a tumor considered high risk.
- Three patients in our series had undergone quarterly clinical and radiological monitoring, only one case died, the 2 remaining patients were lost to follow-up, and the short monitoring period does not allow the evolution to be judged. and the possibility or not of tumor recurrence.

Discussion

Epidemiology

Intestinal localization is the second most frequent localization of GIST (20-30%), after the stomach which is the most frequent (60-70%). The colon, the rectum or the esophagus represent less than 10% of gastrointestinal stromal tumors [9,10,11]. Gastrointestinal stromal tumors represent less than 1% of digestive tumors. However, these are the most frequent mesenchymal-type tumors of the digestive tract (80%) [12] entitynosological. Moreover, the asymptomatic forms are frequent and therefore undiagnosed, and the studies are retrospective [9].

Clinical

Stromal tumors of the small intestine can remain asymptomatic for a long time, their discovery is often fortuitous. Clinical signs and complications usually appear when the volume of the tumor is large. This mode of revelation represents about 20 to 30% of diagnoses and the discovery takes place mainly during a CT scan or abdominal surgery [13-15].

The size of the tumor plays an important role in the occurrence of symptoms: In the case of asymptomatic tumors, an average diameter of 1.5 cm is found compared to 6 cm for symptomatic tumors [16].

In general, small bowel stromal tumors are often revealed quite late with a larger average size and more frequent metastases at the time of diagnosis. They appear most frequently in the jejunum, followed by the ileum and then the duodenum. The main symptoms found are: digestive bleeding, atypical abdominal pain, transit disorders, palpation of an abdominal mass or even a complication such as perforation or intestinal obstruction [17].

For our series, the appearance of an abdominal mass was the most frequent sign of discovery (present in 2/3 of the cases), followed by abdominal pain, digestive bleeding (melena), and a deterioration in general condition.

It is currently considered that all gastrointestinal stromal tumors have some potential for malignancy and may have a

metastatic course [9,10]. Their dissemination is mainly loco-regional and results in hepatic or peritoneal metastases. Lymph node involvement and pulmonary or bone metastases are very rare [9].

The evaluation of malignancy is based on clinical and anatomo-pathological criteria (localization, size and mitotic index), making it possible to classify them in terms of risk [10,18-20]. The discovery of metastases during the diagnosis and the risk of malignancy directly influences therapeutic management. In our series, the assessment of extension in search of metastases was carried out in all our patients, only one case presented liver metastases. Stromal tumors of the small intestine may remain asymptomatic for a long time or present with nonspecific symptomatology. Their discovery and care is sometimes done in an emergency context.

A retrospective study of 92 patients with stromal tumors who were admitted urgently for complications between 2005 and 2012 concluded that the small bowel location appears to be the most at risk of complications. This study revealed that the most common complication was gastrointestinal bleeding (48.9%). The other complications were intestinal obstruction (28.3%), intraperitoneal hemorrhage (15.2%) and tumor perforation associated with peritonitis (7.6%) [21].

Paraclinical Diagnosis

GISTs can occasionally be demonstrated by standard or barium X-rays by revealing an intraluminal mass. Upper or lower endoscopies are useful in the diagnosis of gastric or colonic GISTs and often make it possible to make a diagnosis on their appearance in the event of intraluminal growth. But the examination of choice in the diagnosis and assessment of GISTs is the CT-scan. [22] The CT image is generally typical enough to allow preoperative diagnosis with sufficient certainty. GISTs present as a well-circumscribed mass growing extraluminally, or intraluminally, appearing to be attached to the digestive wall. They are generally heterogeneous, often containing areas of necrosis and richly vascularized. [22] In addition, the abdominal CT scan is important in the pre-treatment work-up for the search for secondary locations (mainly hepatic or peritoneal metastases). Biopsies are not formally indicated due to their low sensitivity and specificity in addition to running a significant risk of hemorrhage for the patient and exposing him to a risk of tumor dissemination. The PET-scan can be useful for patient follow-up because GISTs are often tumors with high contrast uptake (18 FDG), but after a period during which this examination has raised great hopes for the diagnosis and follow-up of patients, the CT-scan has taken over the place of examination of choice for the assessment and follow-up of patients with GIST [23].

Anatomopathological Study

Based on histological and immunohistochemical criteria, most digestive sarcomas, formerly classified as leiomyomas, leiomyoblastomas, leiomyosarcomas, are currently recognized as GISTs. [24,25] GISTs are tumors that develop at the expense of precursor cells of the pacemaker cells of the digestive tract which have the particularity of being c-KIT positive [3]. The c-KIT is a gene responsible for a tyrosine kinase receptor (KIT or CD117) which is largely involved in the etiogenesis of GISTs. [26] The majority of GISTs (L90%) develop following a mutation of the c-KIT gene causing activation of the KIT receptor taking off in autonomous cell proliferation. Familial types of GIST have also been described following germline mutations of the c-KIT gene. [27] Although c-KIT mutations are involved in the etiogenesis of GISTs, they do not seem to play a role in the malignant evolution of these tumors which would be attributable to the occurrence of additional mutations affecting other oncogenes. [28] There are rare cases of negative KIT GIST (approximately 5% of cases), without a mutation of the c-KIT gene, a large part of these have mutations of the PDGFR-A (platelet derived growth factor) gene which is another tyrosine kinase receptor strongly similar to the KIT receptor. [28] Macroscopically, GISTs are pseudo encapsulated tumors, even malignant GISTs, GISTs, often containing foci of hemorrhage and necrosis. They are often associated with ulcerations of the mucosa covering them, explaining their mode of presentation in the form of digestive hemorrhages. Microscopically, these are uniform proliferations of mesenchymal cells which have the particularity of being generally strongly positive in immunohistochemistry for c-KIT (CD117). For their histological and immunohistochemical diagnosis, other markers are used and necessary such as CD34, but the review of which is not the subject of this article [3, 25].

Prognostic Factors

GISTs have the particularity of showing different degrees of malignancy. Among the most recognized prognostic factors, two seem to play a major role: the rate of intratumoral mitosis and tumor size. These two criteria are also the basis of the prognostic scale currently used for GISTs (Fletcher scale) [1]. The five-year survival rate for patients with low-grade GISTs is more than 95 % after surgical resection and is comparable to that of the normal population. In comparison, that of patients with high-grade GIST was 20% five years before the introduction of Glivec [7].

Treatment

A-Surgical Treatment

Radical resection is currently the preferred treatment for GISTs of the small intestine. The sufficiency of radical resection is assessed based on borderline status and complete resection without overflow or rupture of the tumor [29,30].

Tumors with a diameter greater than or equal to 2 cm have the potential for malignancy. From an oncologic perspective, limited resection of small bowel GISTs is an ideal surgical approach [31].

Complete resection of the tumor without large margins or lymph nodes, wide negative resection margins, and prevention of tumor rupture and hemorrhage are required. With the development of laparoscopic surgery, the use of laparoscopic surgery in small bowel GISTs has increased. Currently, studies have shown that there is no statistically significant difference in prognosis between laparoscopic surgery and open surgery [32].

Currently, National Comprehensive Cancer Network (NCCN) guidelines recommend the use of laparoscopic surgery for GISTs no larger than 5 cm [33]. But studies by Liao et al demonstrated that laparoscopic surgery should be considered when the size of the tumor is less than 10 cm. Ihn et al. demonstrated that even a mass 10 cm in diameter can be removed through an incision smaller than 6 cm [34].

Tumor pathology is the key factor in relapse, not surgical technique. Thus, if patients have no contraindications to laparoscopic surgery, it may be a treatment option for small and medium-sized tumors [35]. In our series, 5 cases benefited from surgical treatment, with healthy resection limits.

Specific Treatment:

GISTs are highly resistant to radiotherapy and common chemotherapies [7]. Many protein kinases are overexpressed or abnormally active in cancers and play a major role in their development and progression. They thus represent prime targets in the anti-cancer therapeutic arsenal. Imatinib mesylate is a potent and relatively selective inhibitor of tyrosine kinases including c-KIT, c-ABL, PDGFRA and bcr-ABL [1].

The response rate of metastatic GISTs to imatinib mesylate is 60% to 70% with a median patient survival of more than two years [1,7]. Treatment response of patients with GIST is influenced by the type of c-KIT gene mutations, and for some mutations, increasing doses have been shown to improve the rate of responses. It is important to know that all patients with a tumor response to imatinib mesylate will subsequently develop resistance to treatment. It is for this reason that even in a patient with a complete radiological response, a possible surgical sanction must be discussed. Moreover, once Glivec treatment has started, if it is effective, it must be continued for life, because the risk of a tumor outbreak when treatment is stopped is major [7]. In our series, 4 patients had received adjuvant treatment with Imatinib.

Tumor reduction therapy is considered a new treatment for unresectable malignancies. The combination of imatinib and surgical resection has become an essential approach to treat advanced tumors. There has been scant clinical trial evidence for neoadjuvant treatment with imatinib [36].

Conclusion

Stromal tumors are rare tumors but remain the most frequent mesenchymal tumors of the digestive tract, encountered all along the digestive tract from the esophagus to the anus. The demonstration of the overexpression of the KIT protein by immunohistochemical techniques has greatly contributed to improving the diagnostic approach, and the anatomopathological analysis of the tumor currently allows a diagnosis of certainty.

The intestinal location is the second most frequent location of GIST, after the stomach which is the most frequent location. As stromal tumors of the small intestine are often asymptomatic or responsible for non-specific symptoms, their discovery is sometimes made in the context of complications, requiring emergency treatment. Even if these remain rare, some of them lead to a poor prognosis due to tumor rupture.

Several other criteria, including in particular the size of the tumor, the mitotic index, allow an assessment of the risk of recurrence or metastatic evolution, and to guide the therapeutic decision. Management is based on a multidisciplinary approach and relies mainly on surgery (laparoscopic surgery and open surgery), which constitutes the only potentially curative treatment, as well as on imatinib, a tyrosine kinase inhibitor. Research on other therapeutic possibilities as well as the continuation of studies concerning the two main genes in question (KIT and PDGFRA) should make it possible in the coming years to propose an adequate treatment according to the mutational profile of the tumour.

Acknowledgments

None.

Conflict of Interest

None.

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