

Multiple Stromal Tumors in Von Recklinghausen Disease: A Real Diagnostic and Therapeutic Challenge

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Abstract: *Gastrointestinal stromal tumours (GIST) are rare. They usually occur sporadically, or may be part of a pathological framework such as Neurofibromatosis type 1, and Carney's triad. Familial forms exist. GISTs associated with Neurofibromatosis Type 1 differ from sporadic GISTs in terms of epidemiology, clinical, immunohistochemical, molecular biology, prognosis, and therapeutic management. We report the case of a patient with multiple GISTs in relation to Neurofibromatosis type 1, with the aim of outlining the diagnostic and therapeutic difficulties through a review of the literature.*

Keywords: Gastrointestinal stromal tumours, Von Recklinghausen disease, therapeutic challenge

1. Introduction

Neurofibromatosis type 1 or Von Recklinghausen disease is an autosomal dominant genetic disorder caused by a mutation in the NF1 gene coding for a tumour suppressor protein, neurofibromin, which contributes to abnormal cell proliferation and tumour formation. Gastrointestinal stromal tumours appear to be the most common type of malignancy in these patients [1].

In this article, we report on the epidemiological, clinical, immunohistochemical, genetic, therapeutic, and prognostic features of multiple GISTs in Neurofibromatosis type 1 (NF1).

2. Observation

The patient was 60 years old and was admitted to hospital with moderate rectal bleeding and melena complicated by a severe anaemic syndrome with profound asthenia, dizziness and headaches. The clinical examination revealed mucocutaneous pallor with tachycardia at 120 beats per minute. The skin examination revealed lesions in the form of café au lait spots and neurofibromas all over the body characteristic of neurofibromatosis type 1. After blood transfusion, an endoscopic work-up was performed, including an oesogastroduodenal fibroscopy and a colonoscopy which were unremarkable. An enteroscan was performed, showing at least five nodular, hypervascular, isodense, jejunal lesions with intense enhancement at arterial time, fading at late time, three lesions were located in the proximal jejunum, and two others were located in the distal jejunum. The five tumours measured 17, 8, 30, 6, and 5 mm respectively (**Figure 1**). Surgical management was decided. Surgical exploration revealed multiple jejunal tumours of parietal appearance with extraluminal development, the two largest measuring 27 mm in long axis and 18 mm, prestenosing, located respectively at 30 cm and 140 cm from the duodeno-jejunal angle. The other tumours were of sub-centimetre size. Given the multiplicity of tumours, the

surgeon decided to resect the two largest tumours. The surgical procedure consisted of a 10 cm bowel resection, removing the tumour located 140 cm from the duodenojejunal arch, and a wedge-shaped bowel resection, removing the tumour located 30 cm from the duodenojejunal arch, with a terminal bowel anastomosis, without lymph node dissection.

Macroscopically, the tumour at 140 cm was ulcerated. On section, both tumours had a white-beige appearance. Pathological examination of both lesions showed that they corresponded to a spindle cell proliferation with the phenotype of gastrointestinal stromal tumours. Immunohistochemical study showed that the above tumour proliferation intensely and homogeneously expressed c-kit, DOG-1, CD34, and AML smooth muscle actin and did not express desmin and PS100. The mitotic index for the first tumour was estimated to be 2 mitoses/ 50 CFG, and 3 mitoses/ 50 CFG for the second tumour. The postoperative course was straightforward, and no episodes of externalized gastrointestinal bleeding were reported two years after surgery.

3. Discussion

Gastrointestinal stromal tumours (GISTs) are mesenchymal tumours of the gastrointestinal tract that derive from Cajal cells or one of their precursors. They are typically of the CD117 phenotype commonly known as KIT+ (expressed in 95%), and DOG-1+ (expressed in 95%).

Sporadic GISTs very frequently have activating mutations in the genes encoding the receptor tyrosine kinase KIT or PDGFRA [2]. They are rare tumours accounting for 1-3% of gastrointestinal cancers but nearly 20% of small bowel cancers [3]. Their incidence is 10 to 20 cases per million inhabitants per year [4]. They affect young subjects with a predilection for the fifties [5]. There is no gender predominance in large-scale studies [4, 6]. These tumours occur most frequently in the stomach (60% of cases) and in

the small intestine (25%) [4, 5]. Oesophageal, colorectal and peritoneal locations are less common. The clinical manifestations of GIST depend on the location of the tumour, but also on its size and growth kinetics. They are often asymptomatic for a long time, until they become large or cause a complication, and may be discovered incidentally in small tumours [7]. Bleeding is the most frequent revealing symptom; other symptoms include abdominal pain, the discovery of an abdominal mass, an occlusive syndrome, or weight loss. The endoscopic appearance is that of a submucosal tumour covered by normal mucosa. This appearance is not specific, but by virtue of its frequency, it can be used to evoke the diagnosis, particularly in the gastric region. The tumour may be ulcerated at the apex, especially in cases with GI bleeding. Endoscopic biopsies are usually negative, as the tumour grows from the muscularis propria of the gastrointestinal tract [5]. They may be positive when biopsies are taken from an ulceration. The endoscopic video capsule can detect small tumours of the small bowel [8]. It has the same appearance as a standard endoscopy. However, it should not be performed in cases of subocclusive syndrome due to the risk of capsule retention. Double balloon enteroscopy is an examination that can be carried out as a second line of treatment for abnormalities suspected on video-capsule or enteroscan [9]. Abdominal CT may show a well-limited tissue mass with endo or exoluminal development, sometimes with necrosis and cystic cavities, and thus allow a locoregional extension assessment. Echoendoscopy is the best examination for characterising oesogastrroduodenal or rectal submucosal lesions when they are small [6-7]. It allows the elimination of extrinsic compression, whose endoscopic appearance may mimic a submucosal tumour in every respect, as well as the analysis of echo-endoscopic characteristics allowing a presumptive diagnosis of the nature of the lesion, particularly in the case of GIST, lipoma, or aberrant pancreas. Indeed, the echo-endoscopic appearance of GISTs is often typical: hypoechoic, oval, often homogeneous lesion with regular boundaries, developing from the fourth hypoechoic layer (corresponding to the muscularis) (Fig.2) [6-7]. This appearance may be missed in large or exophytic tumours. Echo-endoscopy also allows guided biopsies of submucosal tumours.

Histologically, GISTs are characterised by a large proliferation of mostly spindle-shaped or epithelioid cells. The diagnosis must be confirmed by immunohistochemistry (KIT expression in 95% of cases, usually associated with CD34 expression, present in 60-70% of cases, PS100, DOG

1, Smooth Muscle Actin AML more frequent in the small intestine, +/-h-caldesmon) [10]. Testing for mutations in target genes is only necessary in the case of a histologically suggestive but KIT-negative tumour [10]. If the histological diagnosis cannot be made by these examinations and in the absence of a therapeutic emergency (haemostasis surgery), surgery will be justified and adapted to the assessment of extension, allowing diagnosis and treatment at the same time [11]. Surgery remains a reference treatment for localized forms. Imatinib mesylate (Gleevec®), a tyrosine kinase inhibitor responsible for tumour proliferation, is currently the first-line treatment for metastatic GIST or as an adjuvant after surgery [12]. Chemotherapy has no place in GISTs. The prognosis for a localised tumour depends on its size, histological criteria, mitotic index (number of mitoses per 5mm²), but also on immunohistochemical and molecular criteria. The presence of metastases, locoregional invasion and mucosal invasion are highly detrimental [11].

GISTs in NF1 are different from sporadic GISTs: The risk of developing a GIST is 45 times higher than in the general population [13]. They are characterised by a slight female predominance, multiple and synchronous primary lesions, and a high incidence of a bowel location [13, 14]. Some patients have more than 100 tumours [14]. The size of the tumours varies between 1 and 15 mm [14, 15]. Histologically they are identical to sporadic GIST but with a lower mitotic index [4]. They are often of low grade malignancy [16]. On immunohistochemistry, they strongly express CD117 (C KIT), with variable positivity for AML, CD34, PS100, while they are desmin negative [17]. In contrast to sporadic GISTs, mutations in the KIT and PDGFRA genes are rare [18]. The absence of these mutations is responsible for a lower response to tyrosine kinase inhibitors: Imatinib appears to have no effect on NF1-associated GISTs [19]. Metastatic GISTs in patients with neurofibromatosis type 1 are characterised by a poor prognosis given the poor response to Imatinib [14].

4. Conclusion

Despite their rarity in the general population, gastrointestinal stromal tumours remain quite common in patients with Neurofibromatosis Type 1. Despite their histological and immunohistochemical similarity, these tumours are genetically, therapeutically and evolutionarily distinct.

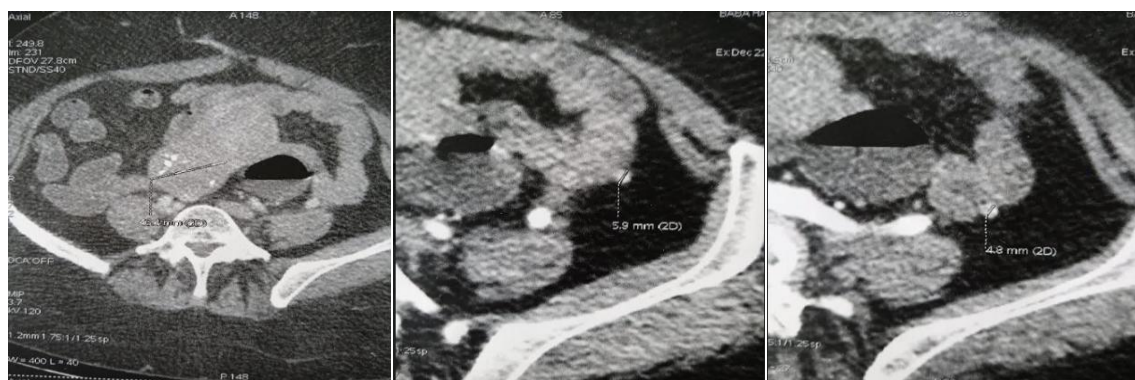


Figure 1: CT scans showing multiple submucosal bowel tumours

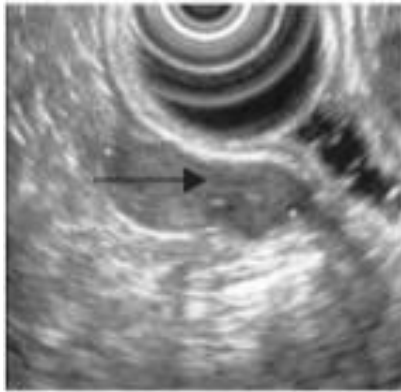


Figure 2: Hypoechoic lesion developing from the 4th hypoechoic layer [9].

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