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Use of Balloon Enteroscopy in Preoperative Diagnosis of Neurofibromatosis-Associated Gastrointestinal Stromal Tumours of the Small Bowel: A Case Report

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Key Words

Balloon enteroscopy · Small intestine · Gastrointestinal stromal tumours · Neurofibromatosis type I

Abstract

Neurofibromatosis type I (NF1) is one of the most common inheritable disorders and is associated with an increased risk of gastrointestinal stromal tumours (GISTs). However, the predominant location of these lesions in the small bowel makes them difficult to diagnose. We report the successful use of balloon enteroscopy in conjunction with conventional methods for clinical diagnosis of jejunal GISTs in a 70-year-old man with NF1 who presented with melaena. The importance of screening NF1 patients for GISTs and the complementary role of balloon enteroscopy with capsule endoscopy in such diagnoses is discussed.

Introduction

Neurofibromatosis type I (NF1), also known as von Recklinghausen disease, is a human genetic disorder characterised by flat pigmented lesions of the skin called café-au-lait spots, combined with peripheral nerve tumours and a variety of other dysplastic abnormalities. It is one of the most common inheritable disorders with an

autosomal dominant transmission and affects approximately 1 in 3,000 people [1]. Clinical expression of NF1 is extremely variable and can include neoplastic or non-neoplastic disorders, mainly with tissues of neuroectodermal or mesenchymal origin in various anatomical locations. Gastrointestinal (GI) manifestations of NF1 are relatively uncommon, but recent studies have indicated an increased risk of gastrointestinal stromal tumours (GISTs) with NF1 [2, 3]. The predominant location of these lesions in the small intestine, however, makes them difficult to diagnose because of the inaccessibility of the small bowel beyond the proximal jejunum with conventional endoscopy methods such as push enteroscopy or small bowel barium follow-through. Recently, a novel endoscopic technique involving balloon enteroscopy (BE) has emerged which enables visualisation of those areas in the small intestine which cannot be reached by traditional methods. Reported herein is a case in whom BE was employed to successfully diagnose multiple jejunal GISTs in a patient with NF1.

Case Report

A 70-year-old man who had been diagnosed with NF1 in his twenties presented to our outpatient clinic with a 2-day history of melaena, fatigue and shortness of breath. There was no family history of NF1. On examination, he was pale with multiple skin lesions, namely café-au-lait spots and soft dermal masses on the trunk and the extremities. Otherwise his physical exam was unremarkable. Laboratory tests showed he was anaemic (haemoglobin 6.0 g/dl), and hence he was admitted and received a transfusion. Oesophagogastroduodenoscopy revealed no lesions. Signs of previous bleeding were detected throughout the colon and the terminal ileum during colonoscopy, but a bleeding source was not identified. Sequential subtraction scintigraphy with ^{99m}Tc -labelled red blood cells was initiated, through which intestinal bleeding was identified and localised at the proximal to mid small bowel. Video capsule endoscopy (CE) also demonstrated blood in the jejunum, but the source of blood loss remained unidentified. Computed tomography was conducted and revealed neither detectable abdominal masses nor evidence of metastatic disease. Therefore, in order to evaluate the entire small intestine, a BE (single balloon enteroscope; Olympus Medical Systems Corp., Tokyo, Japan) was performed, using both oral and rectal approaches. The BE identified multiple submucosal tumours in the jejunum, ranging from 2 to 30 mm in diameter. The largest of them, at approximately 125 cm from the ligament of Treitz, was shallowly ulcerated (fig. 1), supporting the idea that the ruptured tumour was responsible for the bleeding and anaemia. Although the bleeding was initially managed conservatively, due to concerns about the potential risk of re-bleeding the patient eventually underwent partial resection of the jejunum with routine reconstruction.

Gross inspection of the resected jejunal specimen revealed a tumour $28 \times 24 \times 18$ mm in size with a brown-white colour and rubbery consistency. In addition, multiple smaller-sized firm submucosal or submural nodules of a similar appearance were located adjacent to the largest tumour (fig. 2). Microscopically, all tumours were GISTs and consisted of spindle cells forming a vague fascicular pattern (fig. 3a). Immunohistochemical stains of the tumour cells for KIT and CD34 were positive, whilst those for desmin, actin and neurofilaments were negative (fig. 3b–d). The tumour cells showed no mutations in exon 9, 11, 13, or 17 of the *KIT* gene or in exon 12, 14, or 18 of *PDGFRA*. The MIB-1 proliferative index, determined by counting positively stained nuclei among 1,000 tumour cells, was less than 1%, indicative of low mitotic activity.

The patient's postoperative course was uneventful and without any major complications.

Discussion

NF1 is an autosomal dominant disorder with variable penetrance. Genetically, it is caused by a mutation at the *NF1* gene, which is a tumour suppressor gene that encodes the cytoplasmic protein. The protein, called neurofibromin, controls cellular proliferation

by inactivating the p21 RAS and MAP kinase pathways [4, 5]. In addition to cutaneous café-au-lait spots and multiple neurofibromas, various accompanying lesions are known to occur in the eyes, bone, central nervous system and endocrine system [1]. Although GI manifestations of NF1 are relatively less common, recent studies have supposed an increased risk of GISTs [2, 3].

GISTs are mesenchymal tumours that differentiate towards interstitial cells of Cajal or their precursors. These tumours can arise anywhere in the GI tract, from the oesophagus to the rectum, as well as in the omentum, mesentery and retroperitoneum. However, they most commonly occur in the stomach (50%), followed by the small intestine (25%) [6]. GISTs are the most frequently found mesenchymal neoplasms of the GI tract. Still, their incidence is 1.5:100,000 persons per year and they only account for 1–3% of all GI neoplasms [7]. Patients with NF1, however, have a significantly increased risk of GISTs, with an incidence of 5–25% [3, 8, 9]. Although in general most GISTs occur sporadically and multiplicity is very rare, GISTs associated with NF1 have the tendency to be multifocal: approximately 60% of patients have multiple tumours or multiple tumour sites. NF1-associated GISTs also tend to occur more frequently in the small bowel, rather than in the stomach, and tend to be strongly KIT-positive on immunohistochemistry, but in general they are negative for *KIT* or *PDGFRA* mutations [2, 3]. In the present case there were multiple jejunal tumours and they were strongly KIT-positive but lacked both *KIT* and *PDGFRA* mutations, consistent with the established literature on NF1-associated GISTs.

The outcome of NF1-associated GISTs is highly variable and ranges from high-risk tumours with significant invasive or metastatic potential to low-risk tumours that generally remain benign. Several prognostic variables have been identified and include tumour size and mitotic activity. In that context, the GISTs identified in the present case were low-risk, as they were relatively small in size and low in mitotic activity. Nevertheless, it is important to note that a basic tenet is that all GISTs have a malignant potential [6] and therefore can never be considered to be truly benign tumours.

Initial clinical manifestations of NF1-associated GISTs can range from unspecific abdominal pain, early satiety, bloating, palpable abdominal mass, and fatigue from anaemia to bowel obstruction. However, GI haemorrhage, as in the present case, remains the most common presentation [10], and it may either be detected incidentally or present as an acute emergency. While GI bleeding associated with GISTs may be asymptomatic and occult, massive haemorrhage from GISTs is life-threatening and requires immediate treatment.

Given that GISTs are potentially malignant and capable of yielding life-threatening complications, and given that they have a non-negligible incidence rate, it would be fair to say that GISTs remain an important healthcare problem that adversely affects the quality of life of patients with NF1. Hence, it is of clinical relevance to screen NF1 patients for GISTs, although sufficient benefit-risk analyses of the screening programme with this cohort are yet to be reported. Nevertheless, as seen in the present case, these lesions are located primarily in the small intestine, making them extremely difficult to diagnose due to the inaccessibility of the small bowel beyond the proximal jejunum by conventional endoscopy methods. At best, push enteroscopy can be used to visualise the mid jejunum, leaving metres of small bowel distal to this point unexamined. Small bowel barium follow-through lacks the necessary sensitivity. Red blood cell scintigraphy and

angiography may be of use in cases of massive GI haemorrhage, but their use is limited in non- or slowly bleeding patients.

Thanks to recent advances in technology, newer small bowel examination techniques have emerged. CE has heralded a revolution of endoscopic examination by providing a significantly higher diagnostic yield in comparison to conventional endoscopy and small bowel series. CE has also been found to be safe and relatively non-invasive and to have excellent patient acceptance [11]. In the present case, however, while CE disclosed blood in the proximal small intestine, very likely from the bleeding site, it failed to specify the location and the character of the lesion.

Double-balloon enteroscopy, a novel endoscopy technique that employs balloon assistance to allow for real-time visualisation of the entire GI tract, was recently developed. This development was followed by single-balloon enteroscopy, a simplified version which serves as an alternative to the double-balloon approach. In the present case, the jejunal tumours which were initially missed by CE were successfully detected only with BE employed with the single-balloon technique. The reason for this was uncertain, but it was presumably because the tumours were protruding and were submucosal or subserosal in nature, and therefore by using air insufflation and performing to-and-fro movements it became possible to characterise and define them. Such manoeuvres are currently impossible with CE, and therefore BE could be superior in the diagnosis of protruding lesions in the small bowel, as has been suggested elsewhere [12]. Furthermore, another study found CE to have poor inter-observer reliability in terms of detecting abnormalities such as tumours and ulcers, but to be well suited for detecting red-coloured abnormalities such as bleeding and angiodysplasia [13]. Although BE is a lengthy procedure and intrinsically an invasive method of enteroscopy as it is carried out with the patient under sedation, BE is better tolerated and can even be performed as a routine examination. In our institution, patients undergo BE under mild conscious sedation, and the entire small intestine is examined in 1 or 2 steps (per oral and/or per rectal approach).

In conclusion, the present case report supports both the importance of screening NF1 patients with small intestinal GISTs and the effectiveness of BE as a screening modality in such patients. Although CE will likely remain a primary screening tool, considering its overwhelming non-invasiveness, BE can also serve as the complementary approach after an initial diagnostic imaging using CE, and it can overcome the limitations of CE. BE is technically feasible and relatively safe. BE could become a useful screening tool for use in evaluation of the small bowel in patients with NF1, at the very least a complementary method to CE. Future long-term studies and further advances in insertion technique may enhance the role of this procedure as a screening modality in this patient subgroup.

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Disclosure Statement

The authors disclose no conflicts of interest.

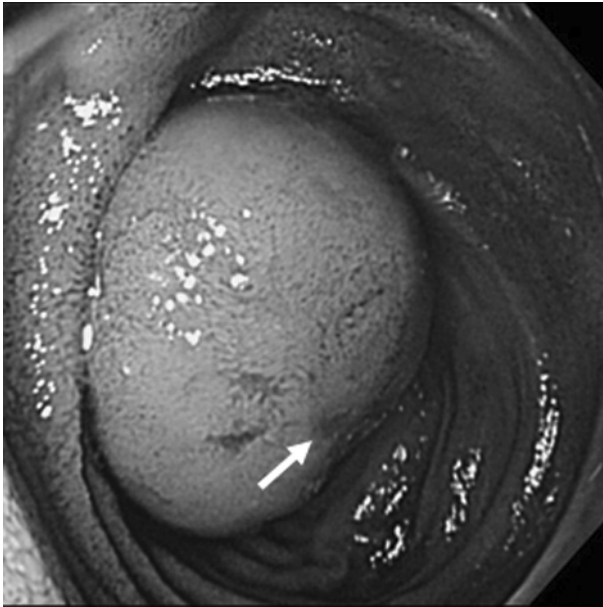


Fig. 1. BE identified multiple submucosal tumours in the jejunum. The largest tumour (arrow) was shallowly ulcerated, indicative of the bleeding source.

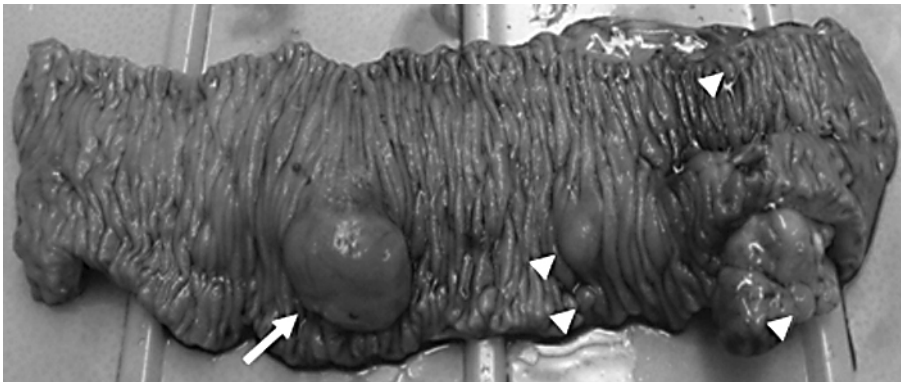


Fig. 2. Gross specimen of resected jejunum showing a tumour with a brown-white colour and rubbery consistency (arrow) surrounded by multiple smaller-sized submucosal and submural nodules (arrowheads).

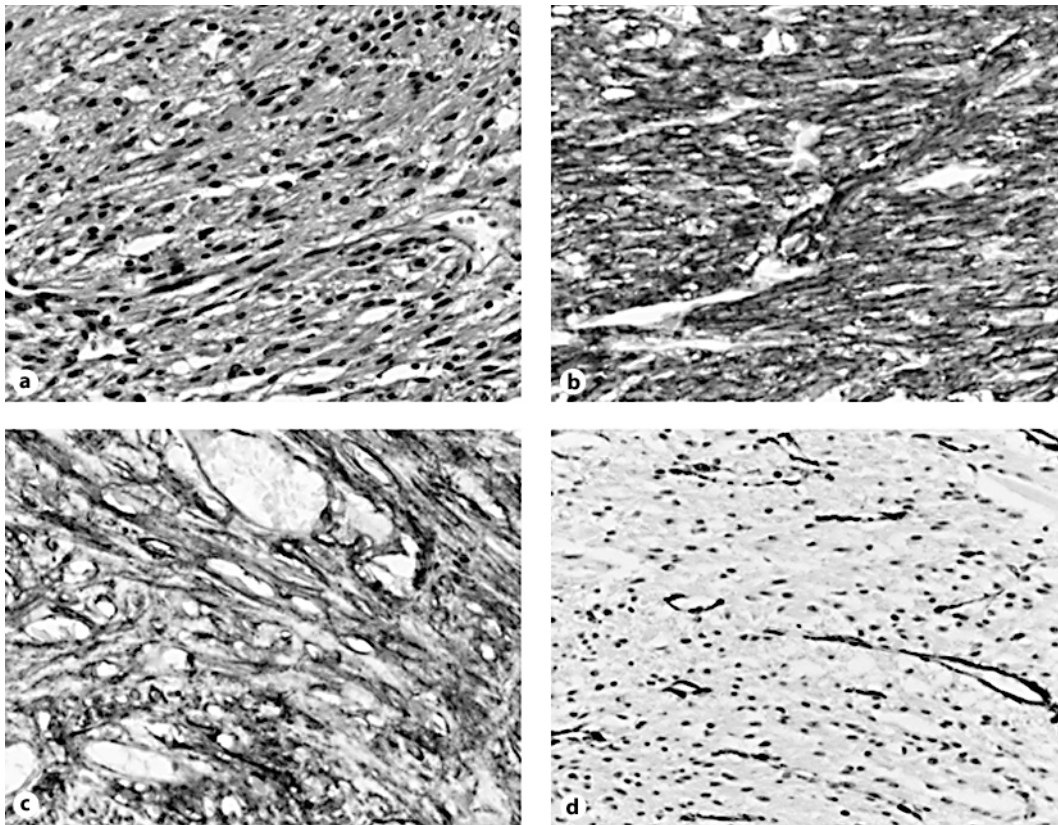


Fig. 3. **a** Histopathology of GIST, consisting of plump spindle cells forming fascicles (haematoxylin-eosin stain). **b–d** Immunohistochemistry of the largest tumour. C-kit (**b**) and CD34 (**c**) were strongly positive, but alpha-smooth muscle actin was negative (**d**). Original magnification $\times 200$.

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