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Single Case

Neurofibromatosis Type 1 Presenting as Bleeding Jejunal Gastrointestinal Stromal Tumour

Raymond Fueng-Hin Liang[a, b] Cora Yuk-Ping Chau[c] Wee Chian Lim[a, b]

[a]Department of Gastroenterology and Hepatology, Tan Tock Seng Hospital, Singapore, Singapore; [b]Lee Kong Chian School of Medicine, Nanyang Technological University, Singapore, Singapore; [c]Department of Pathology, Tan Tock Seng Hospital, Singapore, Singapore

Keywords
Neurofibromatosis type 1 · Gastrointestinal stromal tumour · Gastrointestinal bleeding · Capsule endoscopy · Double balloon endoscopy

Abstract
Introduction: Gastrointestinal stromal tumours (GISTs) are an important, though uncommon, cause of obscure gastrointestinal bleeding and may rarely be associated with genodermatoses such as neurofibromatosis type 1 (NF1). NF1-related GISTs have unique phenotypic features compared with sporadic GISTs and may elude diagnosis due to their predilection for the small bowel. ***Case Presentation:*** We report a case of a 45-year-old Singaporean woman with café-au-lait macules and cutaneous neurofibromas who presented with occult obscure gastrointestinal bleeding and was eventually discovered to have a bleeding jejunal GIST. This finding, considered together with her cutaneous signs, eventually led to the diagnosis of NF1. ***Conclusion:*** Genodermatoses and their gastrointestinal complications are likely under-reported in adult Southeast Asian populations and deserve greater awareness from gastroenterologists practising in this region.

Introduction

Obscure gastrointestinal bleeding is an under-recognized clinical entity with potentially significant morbidity. Bleeding aetiology may be inferred from patient characteristics such as age and comorbidities.

Gastrointestinal stromal tumours (GISTs) are the most common mesenchymal neoplasms of the gastrointestinal tract and are an under-recognized cause of obscure gastrointestinal

Correspondence to:
Raymond Fueng-Hin Liang, raymond_fh_liang@ttsh.com.sg

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bleeding, though up to a fifth of patients may be asymptomatic at the time of diagnosis. A rare but important association exists between small intestinal GISTs and neurofibromatosis type 1 (NF1), an autosomal dominant neurocutaneous genetic disorder with complete penetrance arising from loss-of-function mutations in the *NF1* tumour-suppressor gene on chromosome 17. Current reported literature on NF1-related GISTs is derived predominantly from Western populations, with a paucity of data from Asia.

We present here a Singaporean patient with previously undiagnosed NF1 who presented with occult obscure gastrointestinal bleeding from a jejunal GIST, for which curative resection was achieved. The CARE Checklist has been completed by the authors for this case report, attached as online supplementary material (for all online suppl. material, see https://doi.org/10.1159/000538688).

Case Presentation

A 45-year-old woman attended the emergency department with a 2-day history of syncope, decreased effort tolerance, and subjective "blackening" of her stools. She was a non-smoker without any long-term medications, including non-steroidal anti-inflammatory drugs. She had a past medical history of migraine and iron-deficiency anaemia, for which she presented to another hospital 4 years ago with a haemoglobin (Hb) of 7.0 g/dL and underwent an endoscopy. Esophagogastroduodenoscopy then showed antral and corpus gastritis, while colonoscopy to the cecum was unremarkable. She did not undergo further gastrointestinal evaluation and had a gynaecology follow-up arranged in view of a reported history of menorrhagia.

During the current presentation at the emergency department, she did not have overt gastrointestinal bleeding. Clinical examination was unremarkable, with stable haemodynamics and brown stools on digital rectal examination. Initial investigations were significant for microcytic iron-deficient anaemia (Hb 6.4 g/dL, mean corpuscular volume 58 fL, and ferritin 6 μg/L) with mild thrombocytosis (platelet count 387 × 10^9/L). Serum white cell count, creatinine, urea, liver biochemistry, and coagulation profile were within normal limits. She declined hospital admission and was discharged against medical advice with oral iron supplementation and an early appointment with the gastroenterology clinic.

Upon review at the gastroenterology clinic 4 days later, she remained clinically well. On physical examination, multiple café-au-lait macules and cutaneous neurofibromas were observed over her limbs and back. In view of persistent significant anaemia (Hb 6.3 g/dL), she was given one pint of packed red cell transfusion with an improvement of Hb to 7.4 g/dL, and a repeat endoscopy was arranged the following day.

Esophagogastroduodenoscopy revealed *Helicobacter pylori* (*H. pylori*) gastritis. Colonoscopy showed normal terminal ileum and colon, save for an isolated non-bleeding ascending colon diverticulum. Her Hb normalized to 13.2 g/dL after *H. Pylori* eradication therapy and 5 months of iron supplementation. Following another 6 months of supplemental iron, however, her symptomatic anaemia recurred. Capsule endoscopy was arranged to evaluate for a small bowel bleeding source. This showed a large pedunculated polypoidal lesion with surrounding altered blood in the proximal small bowel (shown in Fig. 1a). Antegrade double-balloon enteroscopy demonstrated an ulcerated subepithelial lesion in the proximal jejunum (Fig. 1b). Endoscopic ultrasound (EUS) with a 15-MHz mini-probe demonstrated a heterogenous hypoechoic lobulated mass without calcifications measuring 28 mm by 17 mm in cross-sectional diameter arising from the muscularis propria layer (Fig. 1c). Abdominal computed tomography (CT) with enteroclysis confirmed an isolated

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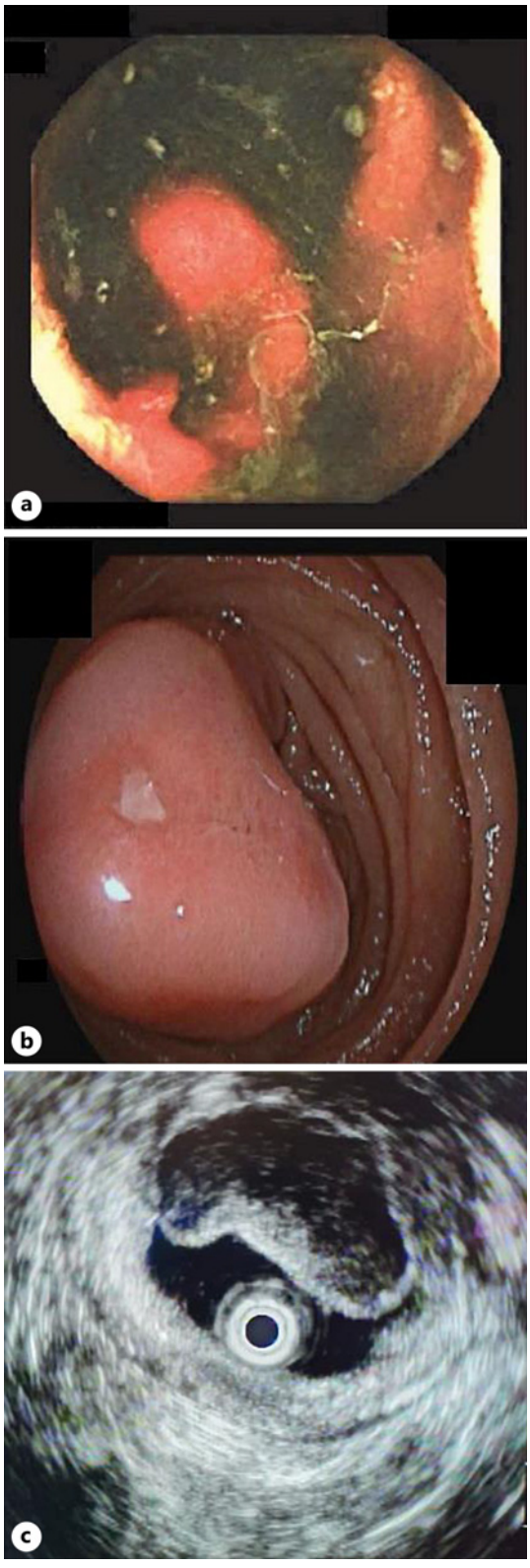

Fig. 1. Images of capsule endoscopy showing a small bowel polypoidal lesion with surrounding altered blood (**a**), double-balloon enteroscopy showing an ulcerated jejunal subepithelial lesion (**b**), and EUS showing a subepithelial lesion arising from the muscularis propria layer (**c**).

submucosal tumour without any other small bowel lesions nor distant lesions (Fig. 2). Incidentally, CT images also revealed a lumbar spinal meningocele and multiple thyroid nodules.

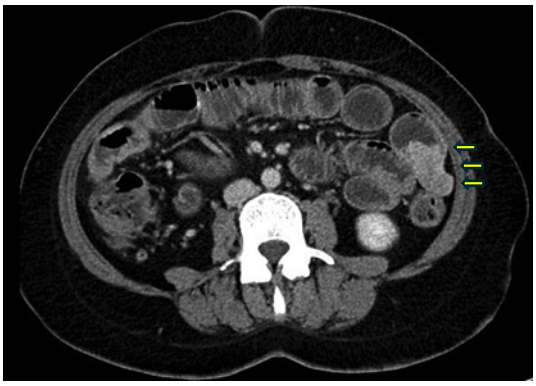

Fig. 2. Axial computed tomography image of an enhancing proximal jejunal submucosal tumour. The arrows show the location of the lesion.

Curative laparoscopic resection of the jejunal lesion was performed. Histopathology demonstrated a 4.2 cm unifocal tumour composed of fascicles of spindle cells with minimal cytologic atypia (H&E, orig. mag., ×200) (Fig. 3a), with immunohistochemistry showing tumour cells diffusely positive for CD117 (c-kit) (IHC, orig. mag., ×100) (Fig. 3b), in keeping with a diagnosis of GIST. Mitotic rate was two per 5 mm^2, and the tumour was deemed low risk. Surgical margins were clear with a final American Joint Committee on Cancer (AJCC) staging classification of pT2N0M0, and adjuvant tyrosine kinase inhibitor (TKI) therapy was not required.

Our patient's Hb normalized to 14.9 g/dL post-operatively. She was referred to dermatology and eventually diagnosed with NF1. She was also seen by neurosurgery and endocrinology for her spinal meningocele and thyroid nodules, respectively, both of which were deemed to be benign and for conservative management. She remains well and recurrence-free on abdominal surveillance imaging on follow-up at 2 years.

Discussion

NF1 patients have variable phenotypic expression and increased frequencies of benign and malignant tumours, the latter encompassing both nervous system tumours and non-nervous system tumours such as GISTs, leukaemias, phaeochromocytomas, and breast and thyroid malignancies [1]. They unfortunately experience excess mortality rates compared to the general population, driven to a significant extent by these malignant neoplasms, with women being more affected than men [2].

Population incidence of GISTs approximates 10–15 per million per year, with a median age of diagnosis in the seventh decade of life and an equal gender distribution. After the stomach, the small bowel is the second-most common location for primary tumours, with the jejunum being the most common location, followed by the ileum and then the duodenum [3]. Most small (<2 cm) GISTs are incidental subepithelial lesions on endoscopy, surgery, or autopsy, with one autopsy series demonstrating an approximately 20% prevalence in individuals above 50 years old [4]. In a systematic review of 46 observational studies comprising 4534 patients, the most common presenting symptom of larger (>2 cm) GISTs was gastrointestinal bleeding with a pooled prevalence of 33% (0–84%), with that of occult bleeding reaching 8.9% (5–85%) [5]. Larger tumour size and a higher mitotic rate are the most important factors adversely affecting prognosis. Other factors associated with a poorer prognosis include small intestinal location, mucosal invasion, ulceration, and high *KIT* expression [6]. In small intestinal GISTs, histologic features such as epithelioid cytology and coagulation necrosis portend a poorer prognosis, while skeinoid fibres and nuclear palisades are associated with a more favourable outcome [6, 7].

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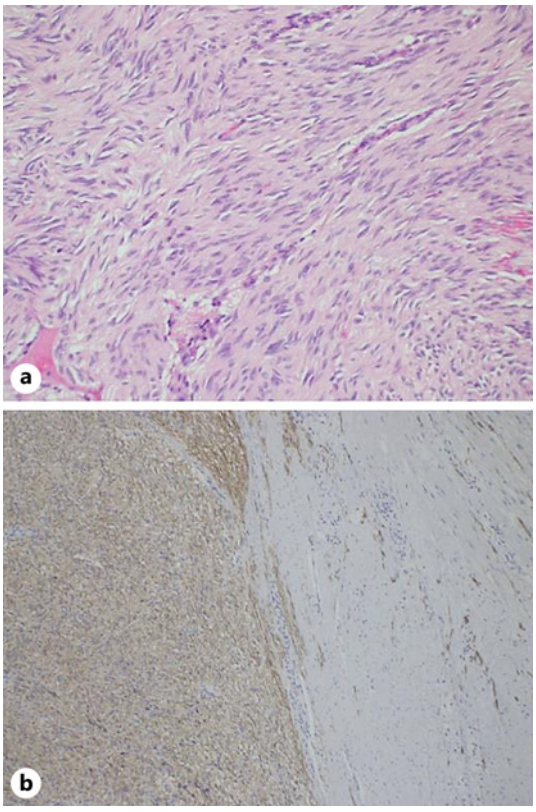

Fig. 3. Microscopic images of a surgically resected specimen showing fascicles of spindle cells with minimal cytologic atypia (haematoxylin and eosin staining, original magnification, ×200) (**a**) and tumour cells diffusely positive for CD117 (c-kit) (immunohistochemistry, original magnification, ×100) (**b**).

EUS is the modality of choice for distinguishing GISTs from other subepithelial tumours and ascertaining high-risk features such as irregular borders, cystic spaces, and lymph nodes with malignant features [8]. Concurrent fine-needle aspiration or core needle biopsies can be taken for histopathological diagnosis and risk stratification, and molecular testing for *KIT* and *PDGFRA* mutations can be performed to assess suitability for TKI therapy such as imatinib. Though the diagnostic rate of EUS-aided tissue acquisition generally exceeds that of stacked endoscopic biopsies, especially for tumours larger than 2 cm, limitations do exist in terms of technical difficulties interrogating smaller lesions and accessibility to lesions deeper in the small intestine and colon. The mucosal unroofing technique has been proposed as a viable alternative diagnostic manoeuvre for selected patients, with a diagnostic rate of up to 72% in a multicentre study of gastrointestinal subepithelial tumours including GISTs [9]. Surgical excision with histologically negative margins is indicated for localized high-risk tumours, with neoadjuvant TKIs considered for tumour downsizing in genotype-sensitive disease to mitigate surgical morbidity. TKIs should also be given as adjuvant therapy for patients at high risk of relapse post-op and are standard therapy for patients with inoperable or metastatic disease [10].

NF1-related GISTs are phenotypically distinct from sporadic GISTs. They occur at a higher frequency compared to sporadic GISTs and are most often found in the distal small intestine [11]. A retrospective cohort study of 1,410 NF1 patients from a population registry showed an overall hazard ratio of 2.6 (95% confidence interval 1.9–3.6) for intestinal tumours in NF1 compared with the general population, with the small intestine having the highest hazard ratio of 15.6 (95% confidence interval 6.9–35.1) in terms of anatomical location [12]. Tumour multifocality is also more common than with sporadic GISTs, possibly related to the diffuse hyperplasia of interstitial cells of Cajal in the myenteric plexus of the small intestine muscularis propria in NF1 patients, akin to that seen in patients with familial GISTs [11, 13]. Most

NF1-related GISTs have spindle-cell morphology and CD34 immunoreactivity. A multicentre study from Japan involving CT screening of 95 clinically asymptomatic adult NF1 patients showed a GIST prevalence rate of 6%, with the tumours having similar clinical and pathological features to those described in Caucasian populations, suggesting a similar NF1-related GIST phenotype in Asians [14]. Data are still lacking, however, for Asian populations, especially in Southeast Asia.

Our reported case exemplifies several unique challenges with the diagnosis and management of NF1-related GISTs. First, there may be a lack of knowledge among clinicians regarding the predisposition of NF1 patients to GISTs. Because of the predilection of NF1-related GISTs for the small intestine, they are usually beyond the reach of routine bidirectional endoscopy. Second, small intestinal GISTs are more likely to present at a more advanced stage by the time they are clinically symptomatic, such as with abdominal pain, gastrointestinal bleeding, or even tumour rupture. Third, small intestinal GISTs generally have a higher risk of malignant behaviour compared to their gastric counterparts of similar size and mitotic activity [6]. Compared with jejunoileal GISTs, duodenal GISTs may have relatively more aggressive behaviour, with metastases occurring even in small tumours with a low mitotic rate in two retrospective series [7, 12]. Despite the present literature suggesting most NF1-related GISTs are indolent with a low mitotic rate [11, 14, 15], it remains uncertain how to reliably achieve early detection of more aggressive tumours based on clinical features. Existing guidelines also do not offer recommendations on screening for GISTs in NF1 patients [10], probably due to their rarity and lack of robust data in this population.

Conclusion

Our patient was fortunate that she presented at a reasonably early stage that still allowed curative surgical resection. Greater awareness of the aforementioned points, however, might have prompted earlier small bowel evaluation and treatment.

Gastroenterologists play a key role in the diagnosis of GISTs in NF1 patients. When detected early, curative resection can be achieved with good outcomes. Abdominal cross-sectional imaging should be considered early in the evaluation of adult NF1 patients with gastrointestinal complaints. Well-coordinated multidisciplinary care with surgeons, radiologists, pathologists, and oncologists is crucial to optimizing outcomes.

Statement of Ethics

This study was performed in accordance with the principles of the Declaration of Helsinki. Written informed consent was obtained from the patient for publication of the details of their medical case and any accompanying images. Ethics approval was not required for this study in accordance with local guidelines.

Conflict of Interest Statement

The authors have no conflict of interest to declare.

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Author Contributions

Raymond Fueng-Hin Liang conceptualized and drafted the manuscript. Cora Yuk-Ping Chau provided histopathological images and expert pathology input. Raymond Fueng-Hin Liang and Wee Chian Lim performed endoscopic investigations. All authors read and approved the final manuscript.

Data Availability Statement

All data analysed during this study have been included in the article and its online supplementary material. Further enquiries can be directed to the corresponding author.

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