Rapid diagnosis of combined multifocal gastrointestinal stromal tumours and coeliac disease in a patient with type 1 neurofibromatosis

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Small intestinal GISTs have a wide variey of presentations and clinical associations which have previously made them difficult to diagnose. The development of newer small bowel imaging techniques in recent years has led to an increased awareness of GISTs as a cause of obscure gastrointestinal bleeding.

Case report

A 65-year-old man with type 1 neurofibromatosis (NF) was referred to the gastroenterology out patient department with recurrent iron deficiency anaemia and a week long history of melaena. His past medical history included ischaemic heart disease, hypertension and asthma. Medications included aspirin and prasugrel. The only positive findings on physical examination were cutaneous neurofibromata.

A serological, haematological screen and tumour markers were all within normal limits. Initial investigations included a gastroscopy, duodenoscopy and colonoscopy; none revealed a source for his anaemia. A small bowel capsule endoscopy (SBCE) revealed an atypical polypoid submucosal lesion in the proximal small bowel with surface ulceration (Figure 1). An anterograde double balloon enteroscopy (DBE) confirmed the lesion; however, it was not amenable to tunnelled biopsy due to extensive surface ulceration. The location was marked with ink to help with subsequent laparoscopic localization. Incidentally, on DBE, there were features suggestive of coeliac disease, which was confirmed by jejunal biopsies (Marsh IIIa).

A magnetic resonance enteroclysis (MRE) was requested prior to laparoscopy which detected a 3.8×3.3 cm suspicious soft tissue mass in the right upper quadrant arising from the small bowel (Figure 2). He proceeded to a laparoscopic-assisted small bowel resection. A large lesion in the jejunum close to the ileum was resected, and multiple additional nodules along the surface of the jejunum were biopsied.

Histologically, the largest tumour was 4.5 cm and a confirmed gastrointestinal stromal tumor (GIST). The expression of c-kit/CD117 and DOG-1 was demonstrated. The mitotic count was <1 per 50 high power fields. The proliferative rate as manifest by MIB-1 expression was <1%. No nodal metastases were noted. Biopsies of the separate nodules (1 cm and 7 mm) also showed GIST with low/absent mitoses.

Following multidisciplinary team (MDT) review, the additional lesions were felt to represent multifocal disease rather than metastases. In accordance with international guidelines, Imatinib treatment was not commenced and regular surveillance was employed. A gluten-free diet (GFD) was commenced. Unfortunately, a follow-up surveillance computed tomography (CT), seven months after surgical resection, showed a 3.5 cm jejunal GIST, representing local disease progression.

Discussion

This case raises a number of interesting issues. The first is the association between NF and

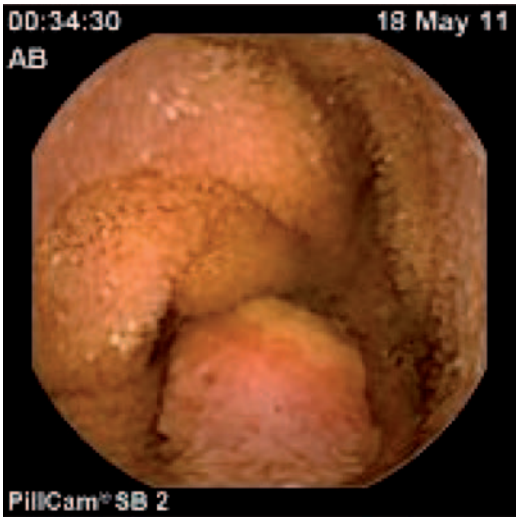

Figure 1. SBCE image of the proximal submucosal lesion.

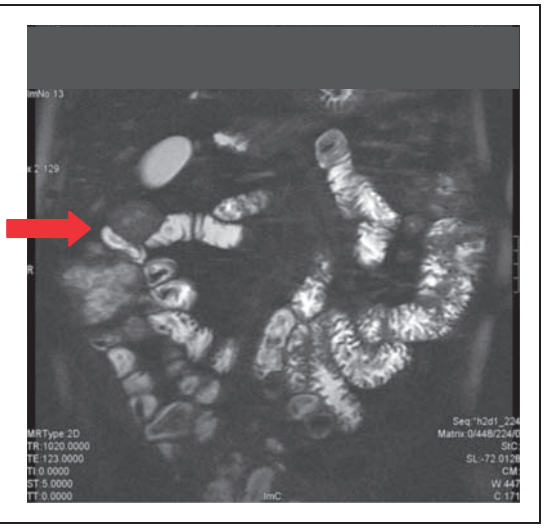

Figure 2. Magnetic resonance enteroclysis showing a 3.3 × 3.8 soft tissue mass.

GISTs and the clinicopathological differences in its presentation compared to sporadic GISTs.

NF is an autosomal-dominant neurocutaneous genetic condition, occurring in two forms, type 1 and type 2. NF patients have an increased risk of developing both benign and malignant tumours throughout their lifetime, due to a loss of function mutation in the NF1 gene, resulting in decreased levels of neurofibromin, a tumour suppressor gene. NF1 is associated with numerous gastrointestinal lesions; hyperplasia of nerve plexuses, GISTs and endocrine tumours of the duodenum and peri-ampullary region.[1] The most common malignancies are central nervous system tumours, but GISTs also occur more commonly in NF patients, who have a lifetime risk of 6%.[2] NF-associated GISTs occur more commonly in the small intestine (60% versus 25% in sporadic GISTs) and are more likely to be multifocal (up to two-thirds) at diagnosis. Histologically, NF1-associated GISTs have a low mitotic rate, and stain positive for CD117 and DOG-1, as in our case, and are generally not associated with the PDGRA mutations seen in sporadic GISTs.[3,4] In addition, multiple lesions in sporadic GISTs tend to be metastatic, while multifocal GISTs are common in three conditions: Carney's triad, Carney-Stratakis syndrome and type I neurofibromatosis. Prognosis of GISTs is determined by tumour size and mitotic count, according to guidelines formed by the NIH 2002 consensus.[5] Applying our case to these guidelines (tumour size 2–5 cm, mitotic count <5 per 50 HPF), he was appropriately deemed to be at low risk for progression and recurrence. The difficulty was in establishing whether his tumour was multifocal or metastatic. In the presence of NF1, a negative staging CT thorax, abdomen and pelvis, and after discussion at an MDT, it was thought most likely that his disease was multifocal NF1-associated GIST, with a low risk of aggressive behaviour. After surgical resection, GISTs have a very variable rate of recurrence, with relapse occurring in 30–50% within five years, and even earlier in high-risk patients.[6] Imatinib, a potent tyrosine kinase inhibitor, works by inhibiting the action of the KIT and PDGFR receptors, which are the main molecular drivers of GIST formation. Phase III randomized controlled trials have shown promising results in increasing median survival rates in patients with high-risk lesions, but there is limited evidence for its use in low-risk patients. A medical oncology meeting on primary GIST management in 2011 recommended that adjuvant therapy should not be used for low-risk patients. There have also been suggestions that NF1-associated GISTs are less sensitive to Imatinib than sporadic GISTs, due to their genetic profile.[7]

Another issue raised in this case is the combined new diagnosis of coeliac disease and GIST.

Coeliac disease is known to be associated with an increased risk of malignancy. Enteropathy-associated T-cell lymphoma (EATL) is the most common malignancy and is estimated to occur 40–100 times higher in Coeliacs than in the general population, with 10% being affected by 50 years of age.[8] This risk has been shown to be related to compliance with a GFD, with rates of EATL dramatically decreased in recent years, due to increased awareness and availability of GFDs. Patients diagnosed with coeliac disease at a later age have a greatly increased risk of malignancy as evidenced by a recent Italian study by Silano *et al*.[9] There is also a recognized increased risk of small intestinal adenocarcinomas in coeliac disease and there have been a few case reports of coeliac disease diagnosed following diagnosis of a GIST, raising the possibility of an additional increased risk of GISTs in coeliac disease.[10] Our patient, aged 65 years, was diagnosed with coeliac at the same time as his GIST. The duration of his coeliac disease is unknown and therefore could potentially have been a risk factor for development of a small intestinal malignancy.

Finally, this case highlights the advantages of employing newer small bowel diagnostic techniques early in the management of patients with obscure gastrointestinal bleeding. The diagnosis of small bowel lesions has historically been a challenge. SBCE has revolutionized our approach to small bowel disease since its launch in 2000 being highly effective, non-invasive, patient friendly and often obviating the need for multiple radiological investigations with lower diagnostic yields. DBE is also a relatively new modality for small bowel pathology. More invasive than SBCE, it has higher risks. The advantage in diagnostic yield over conventional imaging techniques is similar to SBCE. However, its therapeutic capabilities throughout the entire length of the small bowel, including tattooing as undertaken in this case, are a significant advantage and combined SBCE with subsequent targeted DBE offers a new paradigm for the management of a variety of small bowel disorders.

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