

Non-steroidal anti-inflammatory drug-induced diaphragm disease: an uncommon cause of small bowel obstruction

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ABSTRACT

Surgeons frequently deal with small bowel obstruction. However, small bowel obstruction caused by non-steroidal anti-inflammatory drug (NSAID)-induced diaphragm disease is very rare. The diagnosis is challenging, as symptoms are often non-specific and radiological studies remain inconclusive. We present a case of a 63-year-old man who, after an extensive diagnostic work-up and small bowel resection for obstructive symptoms, was finally diagnosed with NSAID-induced diaphragm disease as confirmed by histology. An unusual aspect of this case is that the patient stopped using NSAIDs after he was diagnosed with a gastric ulcer 2 years previously. This suggests that NSAID-induced diaphragms of the small bowel take some time to develop and underlines the importance of careful history taking.

KEYWORDS

NSAID – Capsule endoscopy – Abdominal pain – Intestinal obstruction

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Case presentation

A 63-year-old man presented with intermittent mid-abdominal cramping pain, a loss of appetite and 10 kg weight loss over a few months. He denied vomiting or dysphagia and his stools were loose with no evidence of rectal bleeding or melæna. Past history included osteoarthritis for which he had been taking ibuprofen 400 mg three times daily. However, he had stopped this 2 years earlier following the diagnosis of a gastric ulcer. Laboratory tests revealed anaemia (haemoglobin 8.0 g/dL), hypokalaemia (potassium 3.0 mmol/L) and hypoalbuminaemia (albumin 18 g/L), but normal white blood cell count and C-reactive protein. Repeat gastroscopy revealed a slow-healing prepyloric gastric ulcer (*Helicobacter pylori* negative). Colonoscopy was normal but ileal intubation revealed mucosal oedema. Abdominal computed tomography (CT) angiography and CT enterography were normal except for some mild ileal wall thickening. Capsule endoscopy was undertaken and showed multiple small bowel strictures with some associated superficial ulceration (Fig 1). However, the capsule was retained and the patient presented with recurrent episodes of subacute small bowel obstruction. Following resolution of the acute events, the patient was able to take supplementary liquid feeds to regain

weight and general wellbeing. Laparotomy was then undertaken, at which seven strictures within a 30-cm segment of ileum were found. The diseased segment of ileum also displayed some appearances of fat wrapping and there were multiple enlarged mesenteric lymph nodes (Fig 2). Small bowel resection with primary anastomosis was performed and the retained capsule was retrieved.

Pathological examination of the resected specimen showed multifocal areas of mucosal ulceration and epithelial regeneration as well as marked fibrosis and prominent muscular hypertrophy at the site of the strictures (Fig 3a/b). There were ten reactive mesenteric lymph nodes examined. These findings are consistent with NSAID-induced enteropathy and diaphragm disease.

Discussion

The differential diagnosis of stricturing and obstructive small bowel symptoms in the present case included ischaemic enteropathy, small bowel lymphoma, Crohn's disease and NSAID-induced enteropathy and diaphragm disease. The combination of intermittent abdominal pain, weight loss and a non-healing gastric ulcer might suggest mesenteric ischaemia as a possible diagnosis. However, the CT

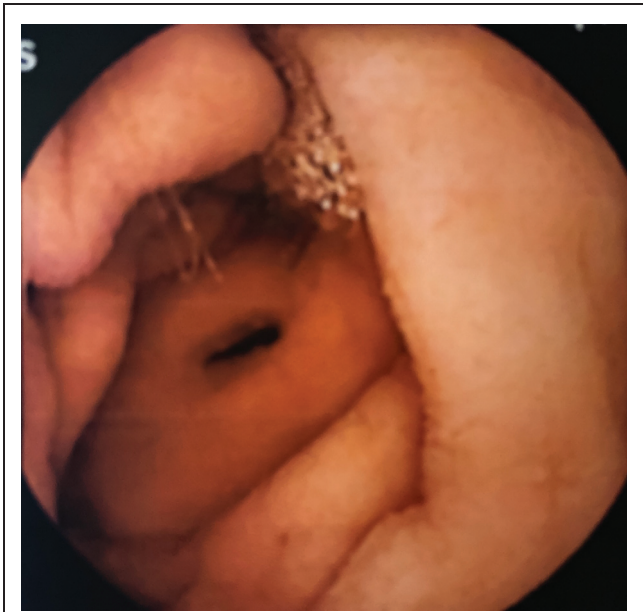


Figure 1 Video capsule endoscopic view showing a small bowel stricture

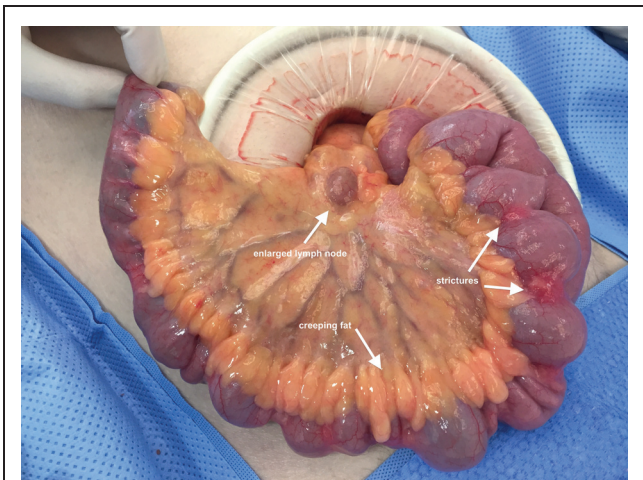


Figure 2 Intraoperative view showing multiple small bowel strictures, enlarged lymph nodes and creeping fat

angiogram did not show mesenteric vessel occlusion and bowel perfusion was normal. Although ischaemic enteropathy can occur without vascular changes (non-occlusive mesenteric ischemia) and post-ischaemic small bowel strictures have been described, this was not likely in the present case.¹

Small bowel lymphoma can also cause stricture and obstruction and can lead to weight loss and hypoalbuminaemia, but this is generally apparent on both CT and capsule endoscopy and can usually be differentiated from other



Figure 3(a) Macrographic photo of normal small intestine on the left and one of the several stenotic lesions on the right

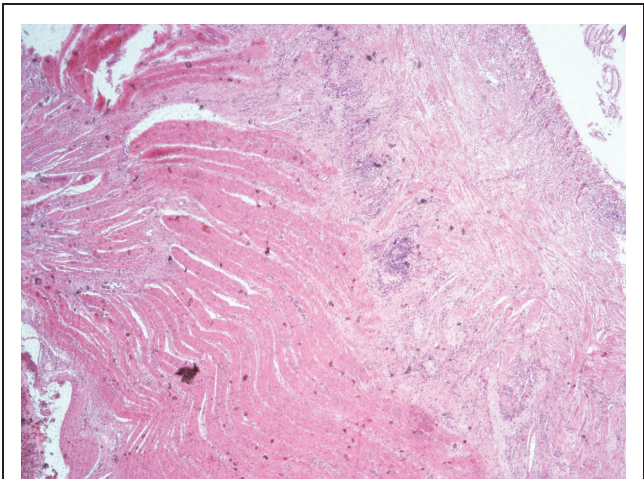


Figure 3(b) microscopic cross-section of stricture showing hypertrophic muscularis propria with vertically orientated muscle fibres and submucosal fibrosis (haematoxylin-eosin stain, original magnification × 20)

diseases. Image-based evidence of multiple segmental circumferential bowel wall thickening is more suggestive of inflammatory disease than lymphoma.²

The morphological appearance of the strictures also fits a diagnosis of Crohn’s disease. Imaging of small bowel strictures caused by Crohn’s disease looks very similar to NSAID-induced strictures. Also, intraoperative findings of Crohn’s disease frequently include ‘creeping fat’ or ‘fat wrapping’, and this was encountered to some extent in the present case, making a diagnosis of Crohn’s disease highly likely. However, there were no pathological features of Crohn’s disease, such as cobblestone mucosa, fissuring, transmural inflammation or granulomas found in the resected specimen and this effectively ruled out a diagnosis of Crohn’s.

The clinical and pathological findings were in keeping with NSAID-induced enteropathy and diaphragm disease. Diaphragm disease is characterised by the formation of thin-

walled strictures (resembling a diaphragm) in the small bowel, which narrow the lumen to a pinpoint and are associated with long-term use of NSAIDs. Although 40–70% of the patients on long-term NSAIDs develop a certain form of small bowel enteropathy, the incidence of NSAID-induced diaphragm disease is only around 2%.^{3,4} This low percentage is likely due to under-reporting, given the fact that many cases remain subclinical with only a very small proportion of patients presenting as a surgical emergency.

The diagnosis is challenging, because symptoms are often non-specific and radiological examinations frequently remain inconclusive. On CT, the diaphragms are often mistaken for peristalsis or Kerckrings folds. Although the diagnosis of NSAID-induced enteropathy has improved with the introduction of capsule endoscopy, there is a risk of capsule retention if strictures are present. If obstruction is suspected, double balloon enteroscopy (DBE) might be a better option; this also has the advantage of allowing biopsies for histology. On the other hand, correct anatomical localisation of the diaphragms is difficult with DBE. Despite these advances, a correct preoperative diagnosis remains elusive in more than 60% of cases.³ Intraoperative diagnosis may also be difficult, as the presented case illustrates, and histological examination is often required to clinch the diagnosis.

Pathogenesis of the formation of diaphragms remains poorly understood. However, it has been suggested that cyclo-oxygenase and prostaglandin inhibition results in damage to enterocytes and villous microcirculation, and the subsequent inflammatory reaction leads to ulceration of the small bowel. Ulceration, which often develops in a circumferential manner, can induce circumferential fibrosis, which in turn is thought to underlie the formation of a diaphragm.^{5,5} Possible risk factors for small bowel injury and diaphragm disease have been identified in a cohort of 156 NSAID users who underwent a DBE or capsule endoscopy. The use of specific NSAIDs (especially diclofenac and the –oxicams), the combination of an NSAID with aspirin and a specific cytochrome P450 29C polymorphism (which causes

a decreased breakdown of NSAIDs), were associated with an increased risk of enteropathy and diaphragm disease.⁴

Management involves cessation of the NSAID and sometimes surgical treatment. At surgery, bowel resection, rather than stricturoplasty, is advocated in the majority of cases. Although high doses of ibuprofen had been consumed by this patient, he had stopped taking the drug 2 years prior to presentation, suggesting that adverse effects on the small bowel, especially fibrotic stricturing, take time to develop.

Conclusion

As surgeons frequently deal with small bowel obstruction, it is important to consider NSAID-induced enteropathy. The incidence of this condition may well rise as a result of a growing elderly population suffering with musculoskeletal conditions, for which prolonged treatment with NSAIDs is indicated. This case highlights the potential importance of NSAID use in patients presenting with anaemia and abdominal discomfort or obstructive symptoms. If obstructive symptoms are present, capsule endoscopy bears a risk of capsule retention and DBE might be a safer way of diagnosing the disease and obtaining material for histological evaluation. Surgical resection is curative provided that NSAIDs are discontinued.

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