NON-STEROIDAL ANTI-INFLAMMATORY DRUG COLOPATHY: CASE REPORTS AND REVIEW OF LITERATURE

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SUMMARY

Non-steroidal anti-inflammatory drugs (NSAIDs) are among the most widely used medication worldwide. Clinicians prescribing these drugs are aware of the contraindications and potentially serious side-effects on the upper gastrointestinal (GI) tract but there is a need for increased awareness and understanding of the effects of NSAIDs on the GI tract distal to the small bowel. Two cases of NSAID-related adverse effects on the colon are reported with a review of the literature. These patients suffered significant morbidity and an avoidable delay in the diagnosis of the condition.

INTRODUCTION

Aspirin was the first NSAID to be synthesised by Felix Hoffman, in 1899. In the second century of their use NSAIDs are among the most widely used medication in the world:[1] more than 30 million people worldwide use them on a daily basis, with a financial outlay of more than $6 billion annually.[2,3] The increasing use of these drugs has become associated with increase in the frequency of clinically significant pathologies due to their side-effects.

The effects of NSAIDs on the stomach and duodenum have been heavily documented over the years, and are well-recognised and understood, enabling much effort to be assigned to preventing these harmful side-effects; the British National Formulary (BNF) highlights these potentially dangerous upper-GI side-effects, and emphasises the need for caution when prescribing this group of drugs. Over recent years there has been an increased reporting of NSAID-related pathology affecting the GI tract distal to the duodenum ranging from inflammation, to ulceration and stricture formation within the small and large intestines. Non-steroidal anti-inflammatory drugs may also complicate further diverticular or inflammatory bowel diseases (IBDs) of the colon.[4] The presence of NSAID-induced small intestine strictures, so-called 'diaphragmatic disease',[5] have been reported since the 1970s.

The increased awareness of NSAID-induced small bowel pathology became associated with a growing concern of similar side-effects distally within the large bowel: the first case of colonic diaphragmatic disease was demonstrated by Sheer and Williams in 1989.[6] Adverse effects of NSAIDs on the healthy colon frequently still remain unrecognised. Furthermore, much less is understood about the mechanism of these NSAID-colopathies. Two patients are presented in which a diagnosis of NSAID-induced colopathy was made.

CASE 1

A 42-year-old Caucasian female, with known Type II diabetes mellitus and fibromyalgia rheumatica presented as an acute admission to our hospital. She gave a five-week history of up to four episodes per day of watery diarrhoea which had resolved spontaneously for a brief period, only to return one week prior to admission. There was no blood or mucus present in the stool. Accompanying this was a three-week history of vomiting and generalised colicky abdominal pain. The presenting symptoms had commenced immediately on return from holiday in Malta. She had undergone a cholecystectomy and appendicectomy 20 years previously. Her medication included nortriptyline 10 mg od, rizatriptan 10 mg prn, diclofenac SR 75 mg bd, metformin 500 mg tds, temazepam 10 mg nocte and co-proxamol prn. She was a non-smoker and teetotal. Physical examination revealed an afebrile patient with pallor, and a diffusely tender, soft abdomen. Rectal examination was normal.

Blood investigations were as follows (normal value ranges in brackets): Hb 10·1 g/dL (11·5–16·5); MCV 79 fL (75–100); WBC $13{\cdot}7 \times 10^9$/L (4·0–11·0); neutrophils $9{\cdot}5 \times 10^9$/L (2·0–7·5); platelets 691×10^9/L (150–400); ESR 100 mm; CRP 59·5 mg/L (<10); and albumin 34g/L (35–53). Urea and electrolytes (U&Es), liver function tests (LFTs), calcium, a coeliac screen, stool and blood cultures, and chest and plain abdominal X-rays were normal. Flexible sigmoidoscopy, colon biopsy and barium enema were both normal. An abdominal ultrasound showed changes consistent with 'fatty infiltration' of the liver. The patient's symptoms improved spontaneously with an improvement in her inflammatory parameters and she was discharged with out-patient review.

On re-admission seven weeks later, she complained of recurrent symptoms of diarrhoea and vomiting as prior to her previous admission, and reported a weight loss of two stone (approximately 12 kg) since returning from Malta. The findings on examination remained unchanged but blood results showed further deterioration: Hb 7·5g/dL, MCV 73 fL, ESR 33 mm, CRP 111·3 mg/L, albumin 16g/L, urea 1·5 mmol/L (2·0–6·9), creatinine 41 mmol/L (44–120). Electrolytes, LFTs and a repeat coeliac screen remained normal.

An episode of coffee-ground vomit on admission

prompted an oesophago-gastro-duodenoscopy (OGD). This revealed ulcerative reflux oesophagitis, diffuse gastritis and a 1·0 cm diameter duodenal ulcer. Duodenal biopsy was normal.

A CT scan of her abdomen showed loops of mildly distended distal small bowel with some localised small bowel thickening in the terminal ileum. As Crohn's disease appeared to be the most likely diagnosis, a colonoscopy was performed. This revealed the presence of three strictures with associated fibrotic and inflamed areas, without ulceration, in the ascending and proximal transverse colon. Two strictures are shown (Figures 1 and 2).

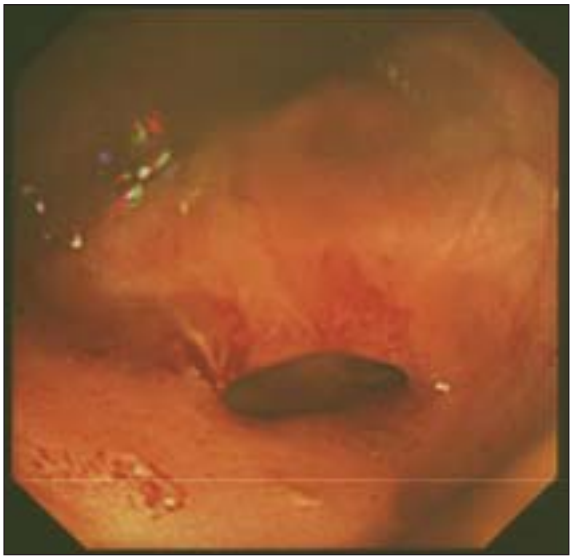

FIGURE 1
Stricture at hepatic flexure.

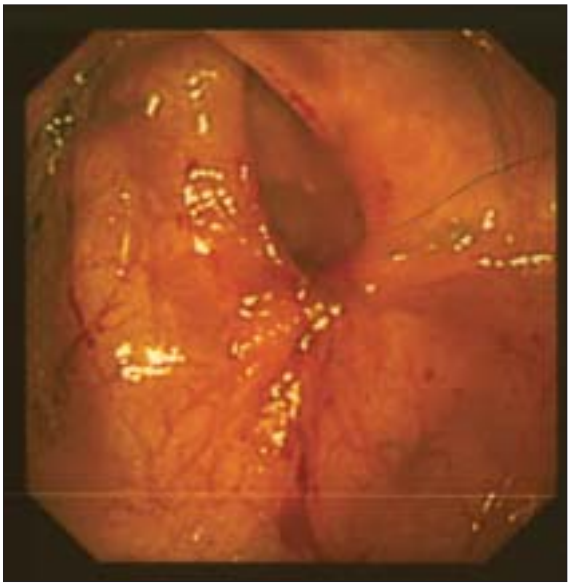

FIGURE 2
Stricture at distal ascending colon.

The most proximal stricture in the ascending colon prevented further progression of the scope into the caecum. Colonic biopsies revealed non-specific appearances of distorted glandular architecture with oedema and slight fibrosis, changes thought to be consistent with quiescent stage of IBD. A further barium enema was performed to visualise the caecum and this raised the possibility of a carcinoma in the ascending colon. Following several days of pre-operative total parenteral nutrition (TPN) therapy, the patient underwent a laparotomy. Although no obvious carcinoma was found, a right hemicolectomy was performed. Macroscopic appearances of the resected colon showed a 5 cm area of narrowing of the ascending colon with flattened and irregular mucosa. There was also a 3 cm x 1·5 cm irregular ulcer in the caecum, with small scattered areas of ulceration throughout the rest of the bowel. Histology confirmed the absence of a malignancy but showed (Figure 3) shallow mucosal ulceration with marked congestion, oedema in the corresponding submucosal tissue and a chronic inflammatory infiltrate.

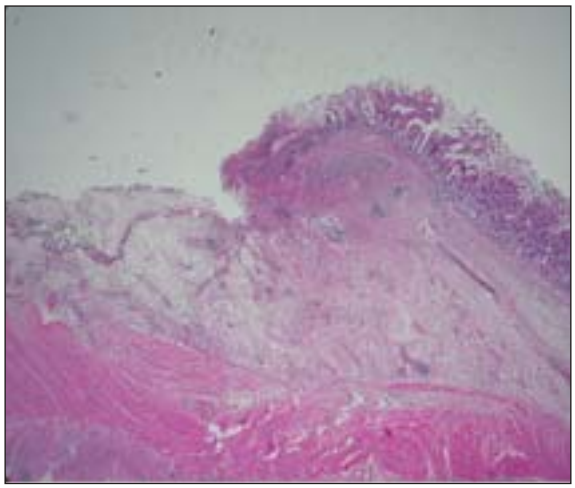

FIGURE 3.
Histological specimen of large bowel ulcer.

No cryptitis or crypt abscess formation was seen. These appearances were thought to be more likely due to a reaction to long-term NSAID exposure.

Post-operative recovery was uneventful and the patient was discharged with advice to keep off all NSAIDs. At out-patient follow-up six weeks later, the patient reported feeling well, and haematological and biochemical parameters had returned to normal.

CASE 2

A 69-year-old Caucasian female, known to suffer from hypertension and depression, presented to hospital with a five-day history of central colicky abdominal pain radiating retro-sternally. There was accompanying vomiting, without haematemesis, and approximately ten episodes of watery/black diarrhoea but with no fresh

blood. The patient was generally unwell for three weeks prior to the admission with poor appetite but reported no weight loss. Her medication included co-codamol (30/500) prn, diclofenac 50 mg tds, risperidone 0·5 mg nocte, zopiclone 7·5 mg nocte, domperidone 10 mg tds, propranolol 80 mg bd, citalopram 20 mg od, loprazolam 1 mg nocte, frusemide 20 mg od and loperamide 2 mg prn. The patient smoked ten cigarettes a day, but had no alcohol intake. Physical examination revealed a febrile patient with temperature of 38·0°C. She looked pale, cachectic and dehydrated. An ejection systolic cardiac murmur could be heard at the aortic area radiating to the carotids. There was generalised abdominal tenderness, especially marked at the left iliac fossa, with no guarding or rebound tenderness. Routine blood investigations were as follows: Hb 6·7 g/L, MCV 96 fL, WBC 9·0 x 10^9/L, neutrophils 5·9 x 10^9/L, platelets 368 x 10^9/L, albumin 32 g/L, urea 8·8 mmol/L, creatinine 148 mmol/L. Liver function tests, a coeliac screen, and chest and plain abdominal X-rays were normal. Ultrasound scan of the abdomen only demonstrated gallstones. A barium enema showed an abnormal configuration to the caecum where, lying inferiorly and laterally, there was a lobulated filling defect, the appearances of which were strongly suggestive of a caecal carcinoma. The corresponding CT scan showed 'fullness' at the recto-sigmoid junction and raised the possibility of a caecal tumour. Her biochemical parameters deteriorated to the extent that she became too ill for a laparotomy. Total parenteral nutrition therapy was commenced.

As no diagnosis had been made, further investigations were performed. Barium meal and follow-through showed a persistent polypoid filling defect in the medial wall of the caecum. A gastroscopy showed a large posterior duodenal ulcer. Colonoscopy was unsuccessful. Therapy was commenced with a 'proton-pump inhibitor' and her NSAID treatment was discontinued. She improved sufficiently for an exploratory laparotomy at which a right hemicolectomy and cholecystectomy were carried out.

The resected colon showed an ulcer, 2·0 cm x 1·0 cm in the ascending colon and a smaller ulcer at the ileo-colic junction. Microscopy (Figure 4), showed superficial ulcers, with the mucosa elsewhere showing slight excess of chronic inflammatory cells, occasional distorted crypts, but no cryptitis. No tumour was identified.

The aetiology of ulceration was not clear, but ischaemia and IBD were excluded. In retrospect, the features were recognised as consistent with a reaction to NSAIDs.

The patient recovered satisfactorily but returned within three weeks with *Clostridium difficile* diarrhoea. With treatment this settled and she was discharged again.

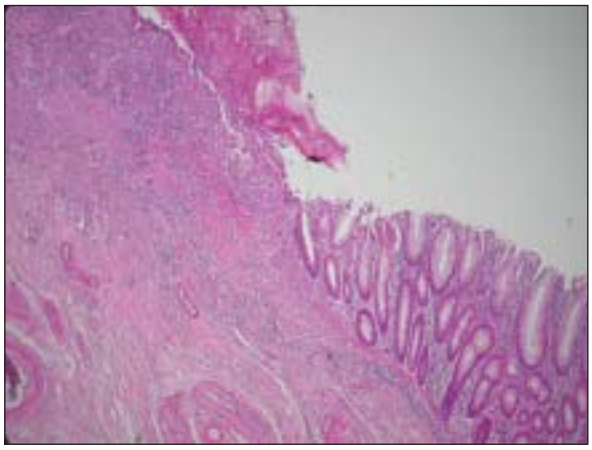

FIGURE 4
Histological specimen of large bowel ulcer.

Follow-up in out-patient clinic confirmed her wellbeing, although she continued to struggle with depression.

DISCUSSION

The chronological description of the illnesses of these two patients highlights and reinforces many of the findings and hazards previously documented in studies and case reports of NSAID-induced colopathy, i.e. delays and inaccuracies in diagnosis. The mechanism of NSAID colopathy has been much debated and aetiological theories abound. Non-steroidal anti-inflammatory drugs appear to increase colonic mucosal permeability, which may lead to ulceration and non-specific inflammatory colitis, as suggested in Figure 5.

Strictures form at sites of healed ulcers as submucosal inflammation matures into collagenous scar tissue. These rings of submucosal fibrosis may contract to form mucosal diaphragms. Colonic ulceration is thought to be one of the early stages of stricture formation.[10,11] Reports of rectal bleeding, ulceration and local stenosis due to the use of NSAID suppository preparations support the direct/topical mode of action.[12] Ulceration and stricture formation predominate within the ascending colon, and are thought to be due to the increased use of slow-release formulations enabling the drug to move further along the GI tract.[13] A stricture has been reported to occur at the site of a bypassed ileal segment which suggests a systemic mode of action.[14] Ulcers can also be induced in murine small intestine on administration of subcutaneous NSAID.[15]

Presenting signs or symptoms of NSAID colopathy include change of bowel habit, weight loss/anorexia, GI bleed/positive faecal occult blood, iron deficiency anaemia and/or abdominal pain. Diagnosis is based on a history of NSAID therapy and appearance of non-specific colitis or ulceration on colonoscopy, which resolves on the withdrawal of NSAID treatment, although strictures do not regress. The appearances of

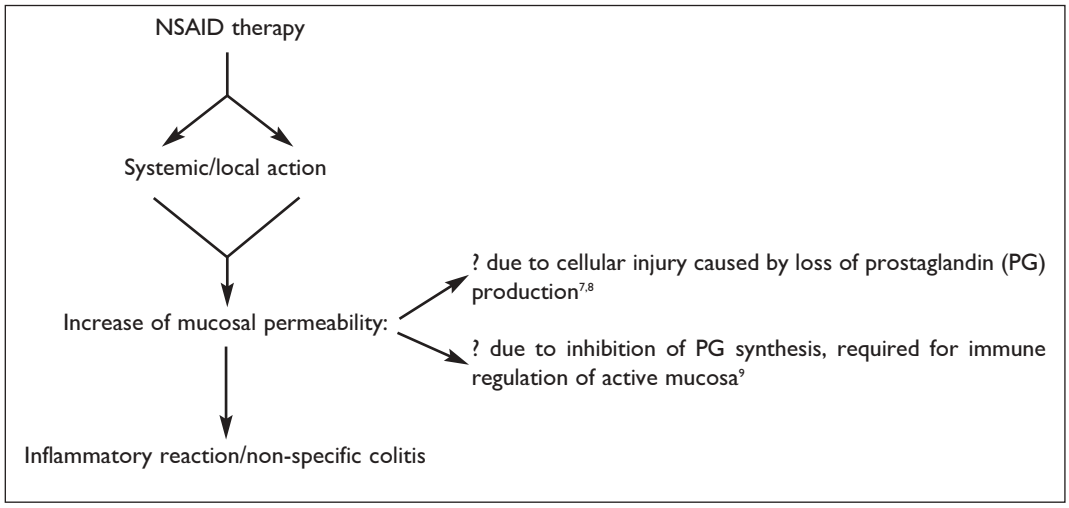

FIGURE 5
Possible mechanisms of NSAID-induced colopathy.

NSAID-induced inflammation/ulceration may lead to a misdiagnosis of IBD at colonoscopy. Histology of biopsy material can help differentiate colitis due to IBD as well as ischaemia and specific infectious agents. A diagnosis of NSAID colopathy should therefore always be considered in patients with indeterminate colitis.

The duration of NSAID therapy is not directly related to the occurrence of NSAID colopathy: short-term therapy can be just as significant, and can occur after only a few days of NSAID use.[16, 17] Progression to stricture formation usually occurs in cases of continuous NSAID exposure for several years.[18, 19]

When strictures are formed, a state of irreversible pathology is reached. These may require balloon dilatation, or even surgical intervention, in addition to NSAID withdrawal.

Evidence for the effectiveness of other medical treatments is limited. Gibson *et al.*[20] suggest the use of steroids as a more aggressive treatment. Faucheron[21] and Bjarnason *et al.*[22, 23] propose the use of metronidazole and/or sulphasalazine in NSAID-induced enteropathy. Patients should also be warned against any use of these medications at any time in the future, even after complete resolution of the disease, since relapse can occur, as documented by Kurahara *et al.*[24] when, 15 months after resolution, relapse occurred almost immediately with use of aspirin.

The recent emergence of specific cyclooxygenase-2 (COX-2) inhibitors has led to significant changes in the medical treatment of many diseases, since these drugs aim to express the benefit of NSAIDs without their side-effects. Wight *et al.*[25] report that, to date, there are no cases of treatment with COX-2 inhibitors increasing gastroduodenal injury or ulceration in humans, but there is still little published work describing any specific effects of COX-2 inhibitors on the large bowel. Freitas *et al.*[26] document a case of acute haemorrhagic colitis after five days of rofecoxib therapy, which resolved after withdrawal of the tablet. Garcia *et al.*[27] document a case of ischaemic colitis following ten days of high-dose meloxicam treatment, which completely resolved within one week of stopping the therapy. More needs to be understood about the effects of COX-2 inhibitors on the colon but in the meantime clinicians should be aware of the potential for side-effects of COX-2 inhibitors on the small and large intestine.

CONCLUSION

There is a need to increase knowledge and awareness amongst clinicians of the effects of standard NSAIDs and possibly COX-2 inhibitors on the colon. Patients will benefit from less confusion and distress when diagnosis of cancer or IBD will not be loosely pinned to NSAID colopathy. More research and understanding into the side-effects of standard NSAID and COX-2 inhibitors on the distal GI tract is needed. The BNF may soon need to be amended to include colopathy as a specific side-effect of NSAIDs.

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