Resolution of multiple severe nonsteroidal anti-inflammatory drug-induced colonic strictures with prednisone therapy: A case report and review of the literature

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A 69-year-old woman on nonsteroidal anti-inflammatory drugs (NSAIDs) was admitted to a university hospital with abdominal pain, profound anemia and melena stools. Duodenal ulceration and subsequent healing were documented. Colonoscopy revealed haustral ulceration and NSAID-induced colonic diaphragm disease. Discontinuation of NSAID therapy did not result in endoscopic change, but a 20-week course of prednisone was followed by complete resolution. This is the first case describing prednisone monotherapy for such strictures, and only the second in which endoscopic resolution has been documented. With further supporting experience, prednisone may be considered in addition to NSAID discontinuation for patients with this rare but serious complication.

Key Words: *Anti-inflammatory agents; Colonic diseases; Non-steroidal; Prednisone*

Guérison de multiples sténoses coliques graves causées par les anti-inflammatoires non stéroïdiens grâce à un traitement par prednisone : Exposé d'un cas et analyse documentaire

Une femme de 69 ans recevant des anti-inflammatoires non stéroïdiens (AINS) a été admise à un hôpital universitaire en raison de douleurs abdominales, d'une anémie profonde et de présence de sang dans les selles. On a observé une ulcération duodénale, qui a par la suite guéri. La colonoscopie a révélé une ulcération haustrale et un diaphragme colique causé par les AINS. L'arrêt du traitement par AINS n'a pas engendré de modifications endoscopiques, mais un traitement de 20 semaines par prednisone s'est traduit par une guérison complète. Il s'agit du premier cas décrit d'une monothérapie par prednisone pour de telles sténoses, et le deuxième seulement pour lequel on a observé une guérison endoscopique. D'autres expériences similaires pourraient servir à appuyer l'utilisation de la prednisone après l'arrêt d'un traitement par AINS chez les patients souffrant de cette complication rare, mais grave.

Nonsteroidal anti-inflammatory drugs (NSAIDs) are commonly prescribed medications with significant toxicities (1). Although they are best known for gastric and duodenal ulceration, they have also been implicated in the development of colonic complications including ulcerations, colitis-like syndromes and complications of diverticular disease (1). Further evidence links NSAID use to the development of collagenous colitis (2-4).

A rare but serious colonic complication of NSAID use is the formation of diaphragm-like strictures, most commonly in the ascending colon at the site of ulcerated haustra. A paucity of published literature exists on NSAID-associated colonic diaphragms, with only 33 cases reported in the English literature (5-26). Case reports have previously documented symptomatic resolution after the discontinuation of NSAID therapy (10,12,15,22,26), after endoscopic dilation (19,21) or after colonic resection (7,8,11,13,15-18,23,26), but data on follow-up colonoscopy or radiology after medical or conservative management is available in only five cases (9,14,15,20,25). Complete healing of diaphragms has been documented only once (20).

This single case of complete stricture healing followed an initial attempt at endoscopic dilation and discontinuation of NSAID use. Because this resulted in incomplete symptomatic and endoscopic resolution after three months, the stricture was redilated and prednisone therapy initiated empirically with complete resolution later observed (20).

In this brief communication, a case is described in which multiple NSAID-associated colonic diaphragms remained unchanged after a trial of NSAID discontinuation and 5-aminosalicylic acid therapy, but healed rapidly and completely with prednisone therapy.

CASE PRESENTATION

A 69-year-old woman developed left lower quadrant pain that gradually intensified over a period of four months. She then began passing two to three melena stools per day for four days and presented to the hospital with ongoing pain, fatigue, weakness and profound anemia. Her symptoms were associated with increasing anorexia and an associated 14 kg weight loss.

Her past medical history included musculoskeletal problems associated with congenital clubbing of her feet and osteoarthritis affecting multiple joints. She also had hypertension and migraine headaches. Although her prescription record indicated multiple medications, she had not filled them all, and admitted to taking only one 325 mg tablet of acetylsalicylic

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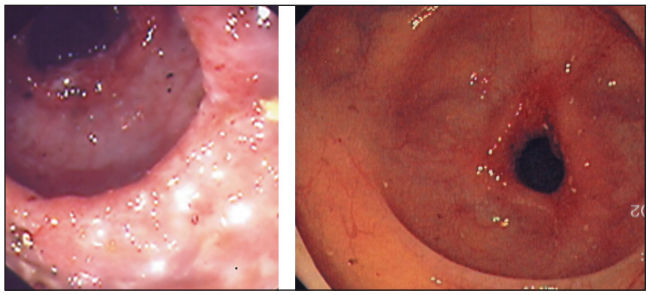

Figure 1) *Note the linear ulceration on the haustral ridges as a precursor for colonic strictures*

acid (ASA) daily, and two to four tablets of Arthrotec (Pharmacia, Canada; 50 mg of enteric-coated diclofenac sodium and 200 µg of misoprostol per tablet) per day. She had been taking these medications in similar dosage for many years. She reported having been investigated at another centre for a single episode of bright red blood per rectum approximately seven years previously. That episode had been attributed to hemorrhoids after she had an otherwise normal colonoscopy. There was no other history of gastrointestinal illness. She had never received radiation therapy and had no family history of inflammatory bowel disease or colon cancer.

Laboratory investigations included a complete blood count that revealed a low hemoglobin concentration of 39 g/L with a mean corpuscular volume of 69 fL, a platelet count elevated at 622×10^9/L and a white blood cell count elevated at 15.8×10^9/L. Her creatinine, electrolytes, liver enzymes and blood clotting times were normal.

Gastroduodenoscopy and colonoscopy were carried out on April 21, 2002, and April 25, 2002, respectively. Gastroscopy revealed a diffusely erythematous antrum and body, which were biopsied and found to be histologically normal with no evidence of *Helicobacter pylori*. On duodenoscopy, four ulcers were found, three of which were clean-based and approximately 1 cm in diameter. The fourth was 3×1 cm in size and had a central elevation but no visible vessel. Her colonoscopy revealed small focal haustral ulcerations and a few diverticuli in the sigmoid colon. The transverse colon was affected by severe circumferential ulcerations limited to the haustra with intervening normal mucosa. Five consecutive haustra were notable for circumferential diaphragmatic narrowings of the lumen to approximately 1.5 cm in diameter (Figure 1). The colonoscope could be just passed through the strictures and the ascending colon was endoscopically normal. Biopsies taken from her colonic ulcers showed ulcers lined by acute inflammatory exudates, consistent with ischemic injury and possibly related to NSAID use. No features of malignancy or Crohn's disease were seen. A small bowel follow-through revealed no other strictures.

During her course in hospital, she was given blood transfusions and oral iron therapy for her anemia, treated with two 40 mg tablets of pantoprazole sodium per day for her duodenal ulcers, and given 4 g/day of 5-aminosalicylic acid in an attempt to accelerate healing of her colonic lesions. ASA and arthrotec were discontinued and her musculoskeletal pain was managed with acetaminophen, glucosamine sulfate and physiotherapy. Her abdominal pain was still present after meals, but its location became more periumbilical. For this reason, repeat gastroduodenoscopy and colonoscopy were performed on May 2, 2002. Her duodenum at this time had some residual areas

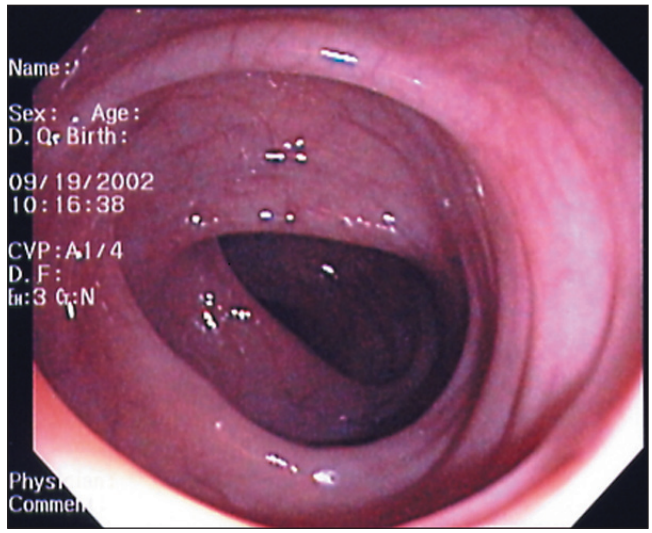

Figure 2) *Healed transverse colon following a 20-week course of prednisone therapy*

of inflammation but there was no ulceration present. Colonoscopy and biopsies of her colonic lesions were essentially unchanged.

Because her duodenal lesions had resolved with no obvious change of her colonic lesions, 5-aminosalicylic acid treatment was discontinued and an empiric course of prednisone was given at an initial dose of 40 mg per day. She was discharged to a convalescent hospital and given intensive rehabilitation in preparation for knee replacement surgery. Because her lower abdominal pain was still present and elective surgery was planned, a repeat colonoscopy was performed May 15. At this time, only two weeks after the initiation of prednisone, her symptoms had improved and there was already significant healing of her colopathy. The left colon was observed to be normal and the strictures of her transverse colon were diminishing. The ascending colon remained normal. Prednisone treatment was decreased to 30 mg per day for two weeks, then 20 mg per day, a dose that was considered safe for her to take perioperatively.

The patient had her knee replacement surgery with further physiotherapy and remained on prednisone 20 mg per day. As the optimal duration of therapy with prednisone was unknown, it was decided to repeat colonoscopy after approximately 17 weeks, a duration adequate to induce healing of other causes of colonic inflammation such as Crohn's disease. After 20 weeks of prednisone therapy, her colonoscopy was entirely normal and there was no trace of her previous ulceration or stricturing (Figure 2). Her hemoglobin had risen since her initial hospitalization and she required no transfusion at the time of her knee replacement. She had no further evidence of gastrointestinal bleeding and had begun regaining the weight she had lost. Her prednisone, which had been taken with no significant side effects, was tapered and discontinued.

DISCUSSION

Colonic diaphragm formation is a rare and poorly understood side effect of NSAID use that can have serious consequences. Many NSAIDs have been associated with this complication, but most followed the introduction of extended-release NSAIDs and a disproportionate number have occurred with enteric-coated diclofenac preparations (1,21,25). Chronic

TABLE 1
Symptoms and signs prompting investigation in patients with nonsteroidal anti-inflammatory drug-induced colonic strictures

Symptom or sign	Cases (%)
Anemia	20 (61)
Abdominal pain	14 (42)
Diarrhea	8 (24)
Weight loss	6 (18)
Anorexia	4 (12)
Nausea ± vomiting	4 (12)
Constipation	2 (6)
Frank hematochezia	1 (3)
Perforated viscus	1 (3)
Abdominal mass	1 (3)

n = 33. Data from references 5 to 26

NSAID-induced colonic ulceration may persist because of antibodies to cyclooxygenase, or the influence of bile acids, bacteria, food antigens or neutrophil chemoattractants (1). Of the 33 previously published cases in the English literature (5-26), the clinical and laboratory features that prompted investigation most often are listed in Table 1. They were most frequent in the right colon (Table 2). The differential diagnosis for the strictures includes Crohn's disease and colon cancer.

Data are scarce on the management and follow-up of this condition. Publications on eight of the 33 previous cases provide no details on treatment or follow-up (5,12,24). Twelve cases were managed with surgical resection (7,8,11,13,15-18,23,26); four with endoscopic dilation (19-21) and nine were managed conservatively by discontinuing NSAID therapy as the sole therapeutic maneuver (6,9,10,12,14,15,22,25).

Surgical resection has been a successful but dramatic method of dealing with these lesions. Of 12 cases, nine had no further complications after resection and discontinuation of NSAID therapy (8,11,13,15-17,23). The remaining three patients resumed NSAID use and experienced new stricture formation (7,18,26). One of these had partial improvement with endoscopic dilation of the new strictures (18) but another failed treatment with endoscopic dilation and required further resection (26).

Of the four cases managed with endoscopic dilation of strictures (19-21), three had symptomatic improvement but no endoscopic follow-up (19,21). The remaining patient continued having abdominal pain for three months and at that time received repeat dilation and treatment with prednisone (20). In this case, prednisone was administered at an initial dose of 40 mg per day with a 5 mg taper each week, and complete endoscopic healing was documented following this eight-week therapy (20).

Of the nine patients managed conservatively by discontinuing NSAID therapy, one had no follow-up (6), three became asymptomatic and had no further follow-up (10,12,22), four had endoscopic or radiological follow-up indicating no change to the lesions (after two weeks, five weeks, 18 months and two years, respectively) (9,14,15,25) and one developed an obstruction relating to the lesion after three months of follow-up (12).

With the limited data available, discontinuing NSAIDs seems to be an obvious first step in patients who develop colonic strictures secondary to the use of this medication. This is supported by the fact that two patients went on to require surgery due to complications of restarting NSAIDs (18,26).

TABLE 2
Locations of nonsteroidal anti-inflammatory drug-induced colonic strictures

Location	Cases (%)
Right colon only	26 (79)
Right and transverse colon	4 (12)
Left colon only	1 (3)
Left and transverse colon	1 (3)
Transverse colon only	1 (3)

n = 33. Data from references 5 to 26

Beyond that, the advice to give patients is not as clear. While surgical resection has been successful, it has significant risks that could be avoided by using medical therapy. Discontinuing NSAIDs alone or in combination with endoscopic dilation has often resulted in symptomatic improvement but has never resulted in healing of lesions on follow-up.

Our choice to use empirical prednisone therapy in this patient was guided by previous animal studies demonstrating that NSAIDs induce acute and chronic inflammatory changes in the intestine, some of which may be attenuated by corticosteroids (27). We were also guided by a previous anecdotal experience of a 49-year-old woman who had been treated with steroids for ascending colonic ulceration thought initially to be Crohn's disease. Subsequent biopsies revealed that her lesions were NSAID-related, but the lesions healed completely after requiring several months of steroid therapy.

Corticosteroids have also had beneficial effects when used intralesionally for strictures elsewhere in the gastrointestinal tract (28-30). In the esophagus, these benefits seem to occur regardless of the initial cause of stricture formation (28).

In the present case, an oral loading dose was used, followed by a maintenance dose for four and a half months, resulting in complete healing. The dosing regimen was adapted from that used to induce remission of active Crohn's disease.

CONCLUSIONS

The literature available demonstrates that patients left with unhealed strictures can develop severe consequences in the form of obstruction or later requirement for surgical therapy (12,26). Furthermore, the follow-up of patients treated conservatively or endoscopically generally reveals no change in their lesions (9,14,15,25). The only previously published case of endoscopic resolution of NSAID-induced colonic strictures followed prednisone therapy after colonic dilation (20), and the case presented here is a successful first trial of prednisone monotherapy. Further experience, and optimally larger studies, with the use of prednisone for NSAID-induced colonic strictures is required to confirm an optimal management strategy, but this case and the previous literature suggest that prednisone can be considered in addition to NSAID discontinuation with or without endoscopic dilation for the management of NSAID-induced colonic diaphragm disease.

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