Rofecoxib associated with diaphragm disease

Michael A. Lapner, MD; Wesley J. Stephen, MD

Small-bowel obstruction secondary to circumferential strictures of the bowel lumen, also known as diaphragm disease, was originally reported as a congenital anomaly. Further research identified that webbing could be caused by other factors, and in 1973 the condition was correlated with nonsteroidal anti-inflammatory drug (NSAID) use.[1] Aspirin has been used as an anti-inflammatory agent for over 100 years, and newer NSAIDs have been used since then. Recently, more selective cyclooxygenase (COX)-2 NSAIDs were released with the intention of minimizing gastrointestinal side effects.[2] The following case report demonstrates an association between the COX-2 inhibitor rofecoxib and diaphragm disease of the small bowel.

Case report

A 52-year-old woman with a history of hysterectomy and rheumatoid arthritis presented in 2005 with recurrent small-bowel obstruction. Six years earlier, her rheumatoid arthritis had been initially treated with celecoxib. She had no history of NSAID use at that time. Her arthritis was unresponsive to the celecoxib, so 1 year later her medication was switched to rofecoxib. She was maintained on 25 mg/day of rofecoxib.

The patient suffered recurrent mechanical small-bowel obstruction beginning 14 months after the introduction of rofecoxib. Because of the chronic bowel obstructions, she underwent a laparotomy 2 years after the introduction of rofecoxib. A small-bowel stricture in the terminal ileum was identified and resected. The surgery was unsuccessful in preventing further small-bowel obstructions. Further investigations carried out at a tertiary centre gave negative results; the investigations included upper and lower gastrointestinal endoscopy and small-bowel imaging.

Because of the recurrent documented small-bowel obstructions, the patient underwent another laparotomy in August 2005. Inspection of the bowel and abdomen revealed no significant abnormalities such as adhesions or serosal pathology (Fig. 1). Intraoperative small-bowel endoscopy revealed an intraluminal stricture (diaphragm disease) (Fig. 2). This was managed with a small-bowel resection. At

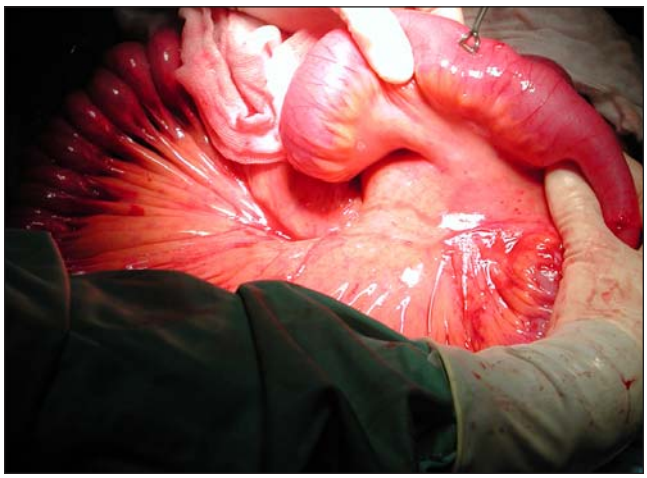

FIG. 1. Normal bowel.

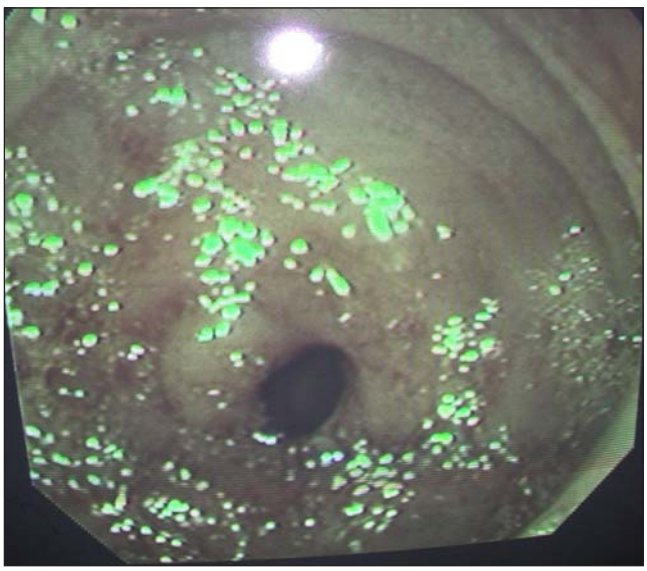

FIG. 2. Endoscopic examination of the small bowel showing an ileal stricture.

Department of Surgery, McMaster University, Hamilton, Ont.

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Correspondence to: *Dr. Wesley J. Stephen, Department of Colorectal Surgery, McMaster University, 1280 Main St. W, Hamilton ON L8S 4K1; fax 905 527-1700; stephenw@hhsc.ca*

follow-up 20 months postoperatively, the patient had had no further bowel obstructions or gastrointestinal symptoms.[1]

Discussion

NSAIDs act biochemically by inhibiting both COX-1 and COX-2 isoenzymes. COX-1 inhibition results in downregulation of prostaglandins, which have gastroprotective effects, and platelet production of thromboxane A_2, which increases hemorrhagic risk.[2] NSAIDs have been shown to cause an enteropathy, which is characterized by increased permeability and inflammation. Chronic inflammation may lead to ulceration and formation of a circumferential septum secondary to submucosal fibrosis.[3] With the advent of a COX-2 selective NSAID, the risk of gastrointestinal and other side effects was hypothesized to be reduced.[4] Cardiovascular side effects resulted in the withdrawal of rofecoxib from the market with the results of the APPROVe trial.[5]

In our report, a woman treated with rofecoxib had diaphragm disease. This suggests that there may be a direct or systemic cytotoxic effect of rofecoxib on gastrointestinal mucosa. Therefore, the selectivity of rofecoxib or other COX-2 medications may not be as effective as hypothesized. By preventing prostaglandin synthesis in gastrointestinal mucosal cells, the end result is stricture formation. The mechanism likely evolves from an initial insult to the bowel mucosa, producing an ulcer followed by subsequent repair through fibrosis. The circumferential nature might, in part, be explained by partial obstruction resulting in physical arrest of a pill, producing a nidus for direct ulceration. If enteric coated, the NSAID would theoretically be prevented from early metabolism, establishing a significant distal bowel ulceration followed by fibrosis. The only other documented report of COX-2 inhibitors and strictures was reported in a case report published in 2004.[6] This study suggested a possible link between a COX-2 inhibitor and diaphragm disease.

This case report suggests a link between the COX-2 inhibitor rofecoxib and small-bowel diaphragm disease. It also reinforces previous claims that NSAID-induced diaphragm disease remains a difficult diagnosis — in our patient imaging, including enteroclysis and plain films, was unremarkable in the work-up of the small-bowel obstruction — and is best identified with endoscopy. Thus, for patients who present with small-bowel obstruction and are using COX-2 inhibitors, the differential diagnosis should include diaphragm disease.

Competing interests: None declared.

References

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