

CASE REPORT

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COX-2 inhibitory NSAID-induced multiple stenosis in the small intestine diagnosed by double-balloon endoscopy

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ABSTRACT

The patient was a 72 year old man who had been given non-steroidal anti-inflammatory drug (NSAID) for two years. He repeatedly developed small intestinal ileus; therefore, he underwent several imaging examinations, but the cause was not identified. He subsequently underwent a double-balloon endoscopy (DBE). The membranous stenoses were detected in the jejunum, and the biopsy specimens were taken during the DBE. The membranous stenoses in the gastrointestinal tract were characteristic of NSAID-induced enteropathy, and he was endoscopically and histopathologically diagnosed with NSAID-induced small intestinal disorder. NSAID administration was withdrawn, and the balloon dilation was conducted for small intestinal stenosis. After that, no small intestinal ileus developed again. Some studies were conducted on the mechanism of NSAID-induced small intestinal dysfunction, but the drug that was administered to the patient was a highly selective NSAID for cyclooxygenase (COX)-2, and there are few studies that reported a dysfunctional mechanism induced by this drug. In the tissue sampled by DBE, apoptotic bodies were found; therefore, it was suggested that the stenoses in this case were caused by the COX-2 inhibitor from the relationship between COX-2 inhibition and apoptosis. Further studies are necessary to investigate the mechanism of NSAID enteropathy.

Key Words: non-steroidal anti-inflammatory drug, double-balloon endoscopy, cyclooxygenase, stenosis

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INTRODUCTION

Non-steroidal anti-inflammatory drugs (NSAIDs) are commonly used for pain control, but their adverse effects can occur throughout the whole gastrointestinal (GI) tract. A close connection between NSAIDs and upper GI injury has been globally accepted. On the other hand, NSAID enteropathy, which develops multiple ulcerations and membrane-like stenosis, is proposed to be a systemic disorder. However, the difficulty of examining the small bowel hampered the identification of such lesions. Double-balloon endoscopy (DBE)^{1, 2} which was introduced in 2001, allows

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deeper insertion into the small intestine. DBE with combined oral and anal approaches can be a modality for examination of the entire small intestine, although it is technically demanding. In addition, DBE enables tissue sampling, polypectomy and hemostasis throughout the small intestine.^{3, 4)} Here, we report an interesting case of cyclooxygenase (COX)-2 inhibitory NSAID-induced enteropathy and membrane-like stenosis who was successfully diagnosed using DBE.

A CASE REPORT

The patient was a male, age 72, whose chief complaint was abdominal fullness. He had been orally given an NSAID (meloxicam: 300 mg/day) for two years due to chronic back pain. He developed an unexplained GI hemorrhage and a small intestinal ileus three times. At the previous hospital, he underwent an upper and lower GI endoscopy, abdominal CT scan and small intestinal radiography, but there were no abnormal findings. Then, he was admitted to our hospital for further examinations. DBE using the oral approach revealed multiple ulcer scars (Figure 1) and pinhole membranous stenoses in the mid-jejunum (Figure 2). DBE using the anal approach produced similar findings in the ileum. In the sampled tissues, reduction of the cervical region in the epithelium and sub-epithelial fibrosis (Figure 3a), including changes in the pericryptal cells to myofibroblasts and collagen hyperplasia, were found. Apoptotic bodies were also observed in the epithelium, and some of them revealed cytolysis (Figure 3b). An ileus caused by multifocal membranous stenosis was the diagnosis. Considering the multifocal stenoses and his high age, balloon dilation was performed using DBE as the first-line treatment. Unfortunately, during treatment, bladder cancer was found; thus, an operation was planned. During the operation, intraoperative enteroscopy balloon dilation was conducted (Figure 4abc), and only one stenosis area that was dilated poorly was partially resected. Six stenoses of the whole small intestine were successfully released. Histopathologic findings of stenosis in the resected specimen showed mucosal erosion, scar formation and slight fibrosis in the submucosal layer without apoptosis. Membranous stenosis in the small intestine, i.e., diaphragm disease,⁵⁾ was caused by the NSAID. We reached a final conclusion of NSAID-induced intestinal membranous stenosis. After diagnosis, NSAID administration was withdrawn, and he has been well without a small intestinal ileus for 3 years after treatment.



Fig. 1 The DBE finding of the ulceration scar in the small intestine.

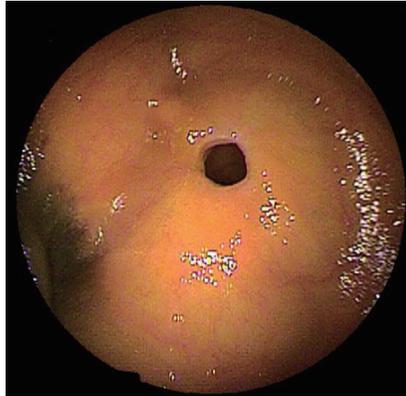


Fig. 2 The DBE finding of the membranous stenosis in the mid-jejunum.

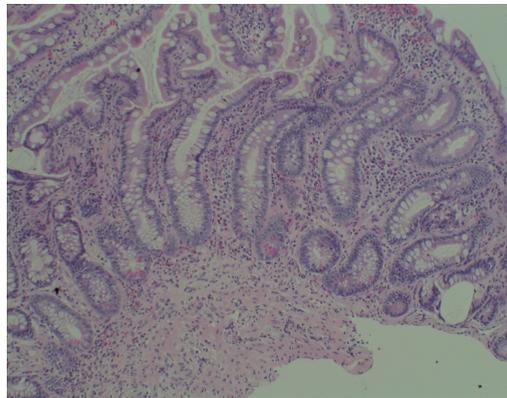


Fig. 3a

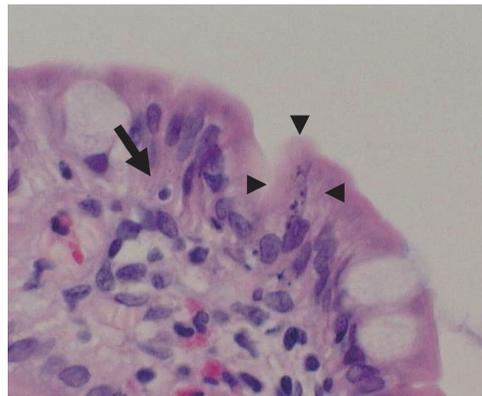


Fig. 3b

Fig. 3 The tissue of the lesion taken by DBE

a: Microscopic finding shows sub-epithelial fibrosis (H&E, 20x).

b: Microscopic finding shows apoptotic bodies (arrow) and cytolysis (arrowheads) in the epithelium (H&E, 200x).

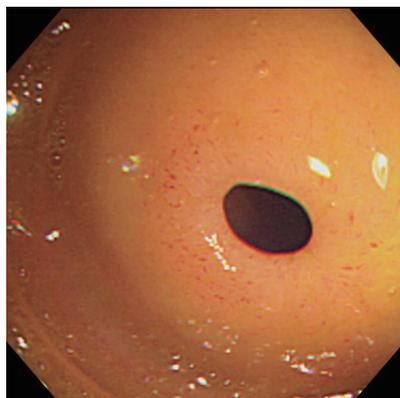


Fig. 4a



Fig. 4b

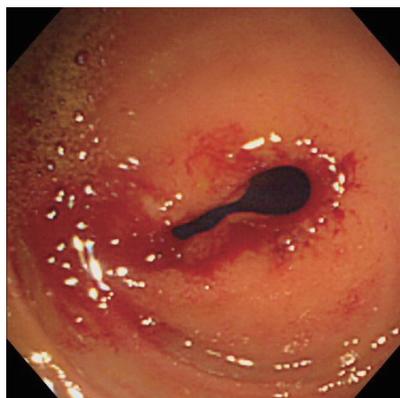


Fig. 4c

Fig. 4

- a: Pinhole stenosis.
 b: Balloon dilation for the stenosis using intraoperative enteroscopy.
 c: After balloon dilation, bleeding was found, and the stenosis was released.

DISCUSSION

The pathogenesis of small intestinal stenosis consists of inflammatory bowel diseases, such as Crohn's disease, intestinal tuberculosis, non-specific multiple ulcers of the small intestine, stenosis associated with vasculitis⁶⁾ and drug-induced injury. Some small intestinal stenoses cannot be identified in spite of many and repeated examinations. In this patient, it was not diagnosed as membranous stenosis of the small intestine until the DBEs were performed. The patient was given an NSAID for a long period; therefore, he was diagnosed with NSAID-induced intestinal stenosis.

Clinical symptoms of this disease are GI hemorrhage, diarrhea, nutritional disorder and stenotic symptoms,⁷⁾ and up to 70% of patients on long-term NSAIDs develop asymptomatic small intestinal inflammation.⁸⁾ The path from onset to diagnosis can take a long time. This patient showed GI hemorrhage and stenotic symptoms, but had not been precisely diagnosed. There are several procedures for the investigation of the small intestine, such as push enteroscopy and sonde enteroscopy, but those procedures have various limitations. Morris reported the usefulness of sonde enteroscopy in NSAID-induced small bowel injury,⁹⁾ but biopsy sampling is not avail-

able. Some patients with this disease require surgical treatment in addition to withdrawal of the NSAID. Macroscopic characteristics of multiple segmental structures, i.e., "string of sausages,"¹⁰⁾ enables diagnosis during the operation. Microscopic characteristics were found that suggested the epithelium in the membranous stenotic region was lost, and the submucosal layer was strongly fibrosed as a pathological characteristic of this disease.¹¹⁾ Additionally, the mucosal folds of the diaphragm were supported by the proliferation of longitudinal bands of thickened and splayed muscularis mucosae extending into the submucosa.¹²⁾ However, the microscopic findings in our resected specimen were different from those in the previous reports. There is the possibility that the microscopic findings of NSAID enteropathy depend on the drug exposure time, the variety of drugs or other factors.

NSAIDs have an extreme anti-inflammatory effect and are used in the treatment for various types of pain. However, adverse reactions can occur throughout the whole GI tract. The probable mechanisms of NSAID-induced injury to the small intestine involve complex pharmacological effects on epithelial cell biochemistry and enzyme function.¹³⁾ Those mechanisms consist of (A) cyclooxygenase (COX) inhibition in the arachidonic acid cascade and decreased prostaglandin production,¹⁴⁾ (B) destroyed mucosal barrier by enhanced permeability of the intestinal mucosa, bacteria-invaded injury and direct injury stimulating the small intestine repeatedly with bile (enterohepatic circulation),¹⁵⁾ (C) free radical production,¹⁶⁾ (D) drug allergy¹⁷⁾ and (E) stress. Ishihara *et al.* suggested that the use of specific NSAIDs and the factors interfering with the metabolism of these NSAIDs might be associated with small intestine injury, especially with diaphragm disease.¹⁸⁾

As for (A), COX-1 is related to tissue maintenance, and COX-2 is involved with inflammation and reproduction. Therefore, NSAID-induced injury was likely to be caused by inhibition of COX-1.¹⁹⁾ Interestingly, meloxicam, a highly selective COX-2 NSAID, caused the injury in this patient. The possible mechanisms were as follows: (a) meloxicam had a weak COX-1 inhibiting effect, (b) COX-2 inhibition also had a strong effect on injury and (c) another possible mechanism. On the one hand, COX-2 inhibition promotes the apoptotic pathway.²⁰⁾ In our case, apoptosis and subsequent fibrosis in the epithelium were histologically observed, suggesting COX-2 inhibition of NSAID-induced apoptosis and suppressed reproduction. One study reported that apoptotic bodies were found in the tissues affected by NSAID-induced colonopathy.²¹⁾ On the other hand, the injury developed only in the small intestine in this patient. NSAID-induced injury might be organ-specific, and furthermore, enterohepatic circulation and bacterial invasion might be involved, such as in (B). In addition, after diagnosis, the NSAID was withdrawn, and the stenosis lesion was removed in an operation three months after finding no apoptosis, which had been found during the diagnosis. From those points of view, in this case, it is suggested that the NSAID caused the injury in the small intestinal mucosa. In conclusion, a highly selective COX-2 NSAID might also cause injury and produce membranous stenosis in the small intestine. In that case, DBE will be useful for a definitive diagnosis.

CONFLICT OF INTEREST

The authors declare no conflicts of interest for this article.

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