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## Diaphragm disease associated with nonsteroidal anti-inflammatory drugs mimicking intestinal tumor: A case report

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## ABSTRACT

**INTRODUCTION:** Diaphragm disease is rare and caused by intestinal obstruction due to nonsteroidal anti-inflammatory drugs (NSAIDs). Given the availability of video capsule endoscopy (VCE) and balloon enteroscopy (BE) this disease will be diagnosed more often.

**PRESENTATION OF CASE:** A 73-year-old man was presented to our hospital for persistent nausea and vomiting. Abdominal ultrasound and computed tomography revealed small-bowel thickening, stricture in the terminal ileum, and dilation of the proximal small intestine. Differential diagnosis included ileal lymphoma and multiple ileal adenocarcinomas, and a diagnostic laparoscopy was performed. Twenty-centimeter of ileum was resected by primary ileo-ileal anastomosis. On pathological examination, fibrosis of the submucosa was identified, and erosions and numerous inflammatory cells reaching the submucosa were also identified from the specimen.

**DISCUSSION:** The preoperative diagnosis of diaphragm disease is sometimes challenging due to its uncharacteristic symptoms; moreover, radiological findings are usually indefinite and distinctive. Currently, the main treatment for diaphragm disease is surgery.

**CONCLUSION:** We have documented a case of intestinal obstruction by NSAIDs. However, it is desirable to determine the course of treatment based on small bowel endoscopic dilatation cases in the future.

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## 1. Introduction

Most clinicians are familiar with the effects of nonsteroidal anti-inflammatory drugs (NSAIDs) on the gastroduodenal epithelium, and there is an increasing evidence of their effects on the distal intestine [1], since video capsule endoscopy and balloon enteroscopy are available for the detection of small intestinal lesion [2–4].

Stenotic lesion was first reported as a diaphragm disease in 1988 [5]. Diaphragm disease is pathognomonic of NSAIDs-induced enteropathy, and is rare.

The term 'diaphragm' describes the rings of collagenous scar tissue, which are positioned like a drawstring across the bowel lumen, inducing the obstruction [6].

Herein, we report a case of small bowel resection for diaphragm disease.

## 2. Presentation of case

A 73-year-old man presented with persistent nausea and vomiting. He had been regularly administering loxoprofen sodium hydrate for years for hip pain.

On admission, he was systemically well with a soft, undistended abdomen and mild tenderness. His routine blood tests were normal except for mild anemia (WBC, 7300/ $\mu$ l; Hb, 10.0 g/dl; Plt, 29.8/ $\mu$ l; Lac, 1.6 mmol/l). Abdominal ultrasound scan revealed the small intestine as dilated and showed areas of narrowing and thickening (Fig. 1). Computed tomography revealed a terminal ileal obstruction with edematous loops (Fig. 2).

An incomplete initial diagnosis of small bowel obstruction from intussusception with ileal lymphoma or multiple ileal tumors was made. Thereafter, laparoscopy was performed. Reddening of the serous membrane and dilatation of the proximal small intestine were observed in the distal ileum, 15 cm from the terminal ileum. The remaining small intestine was normal. Twenty-centimeters of ileum was resected by primary ileo-ileal anastomosis. The patient had a favorable recovery after surgery and was discharged 8 days later.

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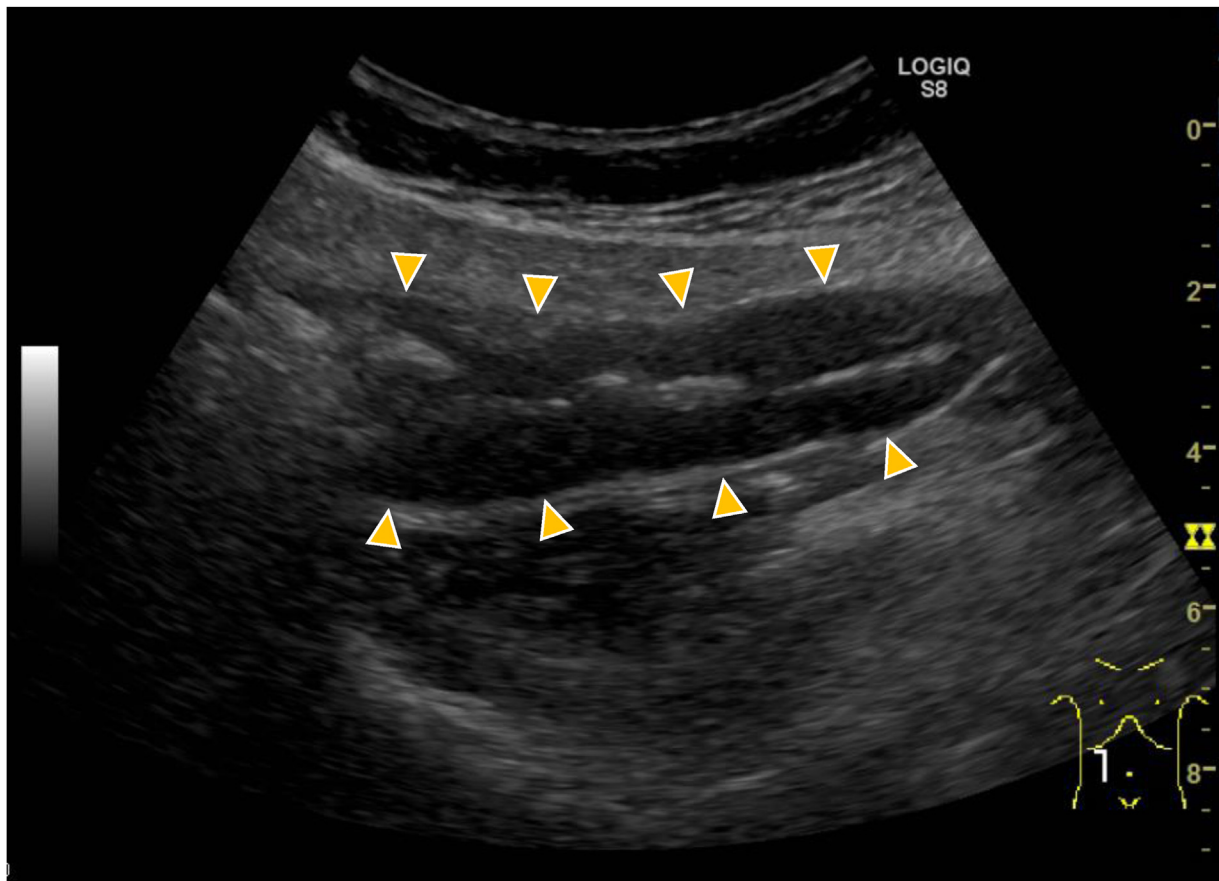


Fig. 1. An abdominal ultrasound scan depicting the dilated small intestine with stagnant contents.

On macroscopic examination, the resected ileum contained a 10 cm long stricture with ulcerated mucosa (Fig. 3).

Stricture histology revealed focal ulceration and numerous inflammatory cells and fibrosis of the submucosa (Fig. 4). Some apoptotic bodies were also observed in the crypts (Fig. 5).

The patient remained well and asymptomatic at a 3-year follow-up.

### 3. Discussion

Studies have demonstrated that more than 50% of patients on NSAIDs experience some mucosal damage in the small intestine [7]. Diaphragm disease is estimated to occur in 2% of chronic NSAIDs users and may cause subacute bowel obstruction in a small subset of patients who have undergone spiral endoscopy [8].

The pathogenesis of mucosal damage has two hypotheses. First, the NSAIDs-induced decrease in prostaglandin production is considered as the cause of small bowel injuries [9–13]. Second, NSAIDs solubilize lipids of the phospholipids on the mucosal surface, such that the epithelial mitochondria are directly damaged. Thereafter, the mitochondrial damage depletes intercellular energy leading to calcium efflux and induction of free radicals, a disruption of the intercellular junctions occurs, and mucosal permeability increases in the small intestinal mucosa. Finally, the mucosal barrier becomes weakened, such that bile acid, proteolytic enzymes, intestinal bacteria, or toxins easily penetrate the epithelial cells, resulting in mucosal injury [13]. In the preparation of the ulcer, fibrosis of the mucosal and submucosal layers forms a diaphragm or mucosal web, with luminal narrowing, consequently, leading to obstruction [14].

Hayashi et al. defined the criteria of NSAIDs-induced small intestinal injuries as (1) history of NSAID use; (2) endoscopic findings of erosion and/or ulcer and/or typical diaphragm-like strictures; (3) improvement in clinical findings (signs and symptoms) and/or endoscopic findings by the cessation of NSAIDs, except for diaphragm disease; and (4) exclusion of other causes (e.g., malignant tumor, inflammatory bowel disease, and infectious disease) [15].

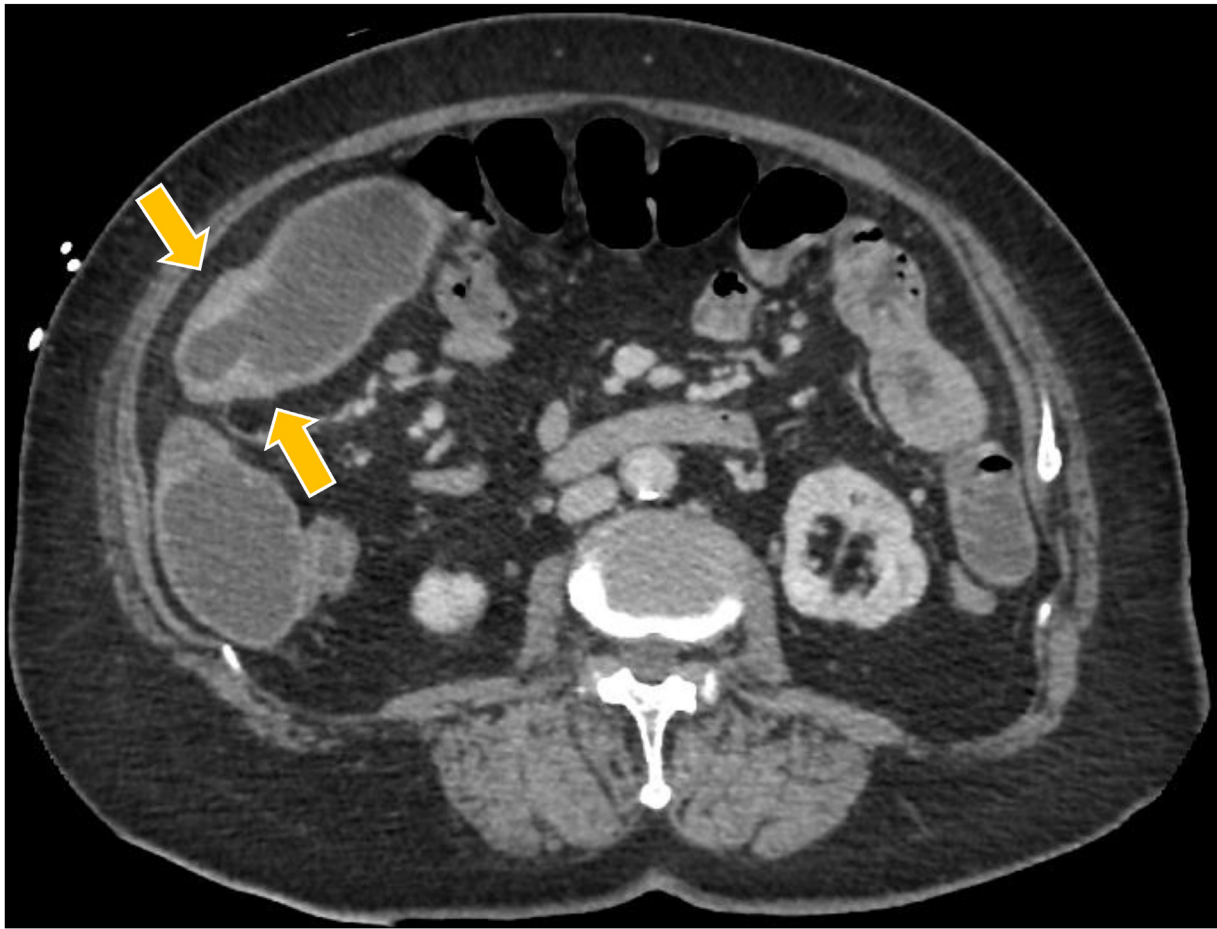
Preoperative diagnosis of diaphragm disease is sometimes challenging due to its uncharacteristic manifestations; moreover, the radiological findings are usually indefinite and distinctive.

Consequently, diaphragm disease is most often diagnosed by exploratory laparotomy followed by histopathological examination of the resected bowel [14]. Additionally, the history of NSAIDs use is required.

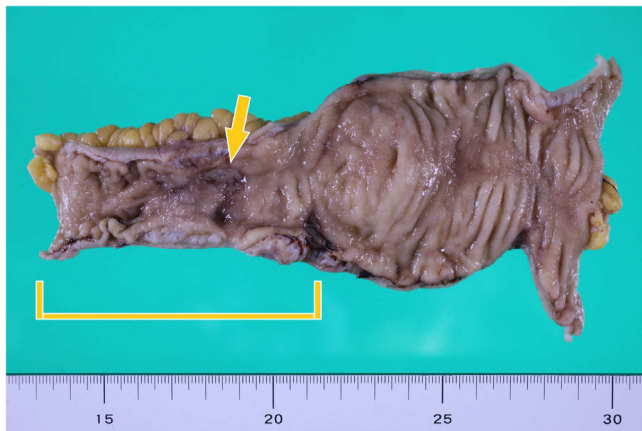
We considered nonspecific multiple small bowel ulcerations, Behcet's disease and Crohn's diseases, that were ruled out because the patient was relatively old, and had no symptoms of inflammatory bowel disease or extraintestinal lesions. The pathology examination did not reveal noncaseating granulomas or tumor cells; therefore, intestinal tuberculosis, ileal lymphoma, multiple ileal carcinomas, or neuroendocrine tumor were ruled out. He had a long history of NSAID medication for his hip pain. These findings were consistent with the criteria (1) and (4) of NSAIDs-induced small intestinal disease.

Treatment of strictures must include surgery and withdrawal of the offending NSAID.

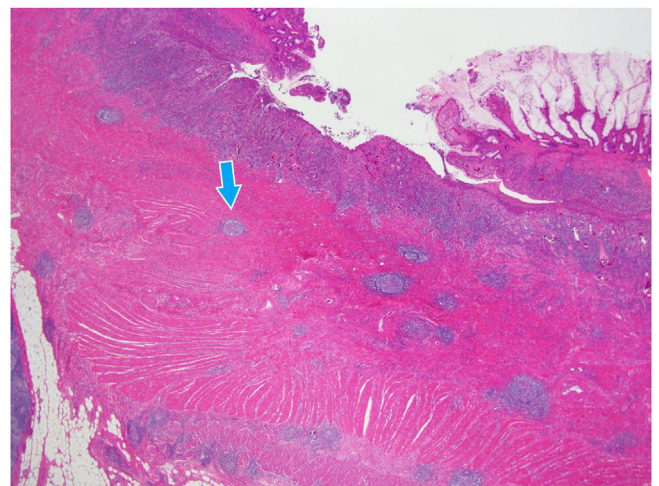
The following drugs considerably inhibited small bowel injuries: lansoprazole, rabeprazole, lafutidine, roxatidine, teprenone, rebamipide, irsogladine, and misoprostol. However, drugs that did



**Fig. 2.** A CT scan showing small-bowel thickening and dilation of the proximal small intestine.



**Fig. 3.** A resected specimen showing stenosis with wall thickening and ulcer (Arrow indicates ulcer.).



**Fig. 4.** Fibrosis of the submucosa and formation of lymphatic follicles in the submucosal and serous layers at the site of stenosis. In the ulcerated area, erosions and numerous inflammatory cells that reach the submucosa. (Arrow indicates lymphatic follicles) (hematoxylin and eosin stain,  $\times 1.25$ ).

not inhibit the injuries were omeprazole, famotidine, cimetidine, ecabiet sodium, and sucralfate [7].

Additionally, diaphragm disease can be treated with enteroscopic balloon dilation to prevent surgery. This is because fibrotic strictures that occur may be limited only to the submucosal layer and, therefore, dilating the bowel may give some relief. Alternatively, patients may be required to undergo surgery and if the patient presents with severe symptoms, this may require an emergency laparotomy [16,17].

In this case, small bowel stenosis due to tumor was suspected at first, and the long-term NSAID use caused inflammation in the deepest part of the intestine to spread to the subserous layer, such that surgery was appropriate.



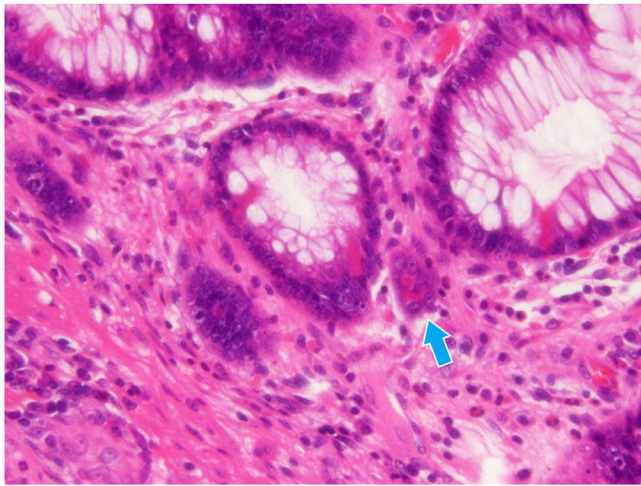


Fig. 5. Apoptotic bodies in the crypts.

#### 4. Conclusion

A case of laparoscopic small bowel resection for small bowel ulcers and scar stenosis caused by NSAIDs. Currently, the main treatment is surgery. However, determining the course of treatment based on the accumulation of small bowel endoscopic dilatation is advisable for cases in the future.

#### Declaration of Competing Interest

The authors report no declarations of interest.

#### Source of funding

None.

#### Ethical approval

This case report was approved by the Kobe City Medical Center General Hospital Review Board (#zn200704).

#### Consent

The consent to publish this case report was obtained from the patient.

#### Author's contribution

AM drafted the manuscript, and HH revised the manuscript critically. DY and TY revised the histopathological findings. All authors contributed to study concept or design at this submission and approved the final manuscripts.

#### Registration of research studies

N/A.

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#### References

- [1] N.M. Davies, J.Y. Saleh, N.M. Skjodt, Detection and prevention of NSAID-induced enteropathy, *J. Pharm. Pharm. Sci.* 3 (1) (2000) 137–155.
- [2] N. Kameda, K. Higuchi, M. Shiba, et al., A prospective, single-blind trial comparing wireless capsule endoscopy and double-balloon enteroscopy in patients with obscure gastrointestinal bleeding, *J. Gastroenterol.* 43 (6) (2008) 434–440.
- [3] H. Yamamoto, Y. Sekine, Y. Sato, et al., Total enteroscopy with a nonsurgical steerable double-balloon method, *Gastrointest. Endosc.* 53 (2) (2001) 216–220.
- [4] K. Sunada, H. Yamamoto, Double-balloon endoscopy: past, present, and future, *J. Gastroenterol.* 44 (1) (2009) 1–12.
- [5] J. Lang, A.B. Price, A.J. Levi, M. Burke, J.M. Gumpel, I. Bjarnason, Diaphragm disease: pathology of disease of the small intestine induced by non-steroidal anti-inflammatory drugs, *J. Clin. Pathol.* 41 (5) (1988) 516–526.
- [6] L. Maiden, B. Thjodleifsson, A. Seigal, et al., Long-term effects of nonsteroidal anti-inflammatory drugs and cyclooxygenase-2 selective agents on the small bowel: a cross-sectional capsule enteroscopy study, *Clin. Gastroenterol. Hepatol.* 5 (9) (2007) 1040–1045.
- [7] K. Higuchi, E. Umegaki, T. Watanabe, et al., Present status and strategy of NSAIDs-induced small bowel injury, *J. Gastroenterol.* 44 (9) (2009) 879–888.
- [8] A. Chernoleskiy, S. Lanzon-Miller, F. Hill, T. Al-Mishlab, Y. Thway, Subacute small bowel obstruction due to diaphragm disease, *Clin. Med. (Lond.)* 10 (3) (2010) 296–298.
- [9] A. Robert, T. Asano, Resistance of germfree rats to indomethacin-induced intestinal lesions, *Prostaglandins* 14 (2) (1977) 333–341.
- [10] W.F. Fang, A. Broughton, E.D. Jacobson, Indomethacin-induced intestinal inflammation, *Am. J. Dig. Dis.* 22 (9) (1977) 749–760.
- [11] B.J. Whittle, Mechanisms underlying intestinal injury induced by anti-inflammatory COX inhibitors, *Eur. J. Pharmacol.* 500 (1–3) (2004) 427–439.
- [12] T. Yamada, E. Deitch, R.D. Specian, M.A. Perry, R.B. Sartor, M.B. Grisham, Mechanisms of acute and chronic intestinal inflammation induced by indomethacin, *Inflammation* 17 (6) (1993) 641–662.
- [13] I. Bjarnason, J. Hayllar, A.J. MacPherson, A.S. Russell, Side effects of nonsteroidal anti-inflammatory drugs on the small and large intestine in humans, *Gastroenterology* 104 (6) (1993) 1832–1847.
- [14] Y.Z. Wang, G. Sun, F.C. Cai, Y.S. Yang, Clinical features, diagnosis, and treatment strategies of gastrointestinal diaphragm disease associated with nonsteroidal anti-inflammatory drugs, *Gastroenterol. Res. Pract.* 2016 (2016), 3679741.
- [15] Y. Hayashi, H. Yamamoto, H. Taguchi, et al., Nonsteroidal anti-inflammatory drug-induced small-bowel lesions identified by double-balloon endoscopy: endoscopic features of the lesions and endoscopic treatments for diaphragm disease, *J. Gastroenterol.* 44 (Suppl 19) (2009) 57–63.
- [16] N. Ohmiya, D. Arakawa, M. Nakamura, et al., Small-bowel obstruction: diagnostic comparison between double-balloon endoscopy and fluoroscopic enteroclysis, and the outcome of enteroscopic treatment, *Gastrointest. Endosc.* 69 (1) (2009) 84–93.
- [17] V.R. Velchuru, D. Rimal, J.G. Studley, H.G. Sturzaker, Diaphragm disease of the ileum, *Int. J. Surg.* 4 (3) (2006) 184–186.

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