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## Case Report

# Retention of Capsule Endoscopy at the Site of NSAIDs-induced Intestinal Ulcer – Lessons to Learn –

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A 77-year-old man with a history of non-steroidal anti-inflammatory drugs (NSAID) use was admitted to our hospital due to anemia and hypoalbuminemia. Radioisotope scintigraphy indicated protein loss from the small intestine. The patient underwent capsule endoscopy, which was later found to be retained in the ileum. Double-balloon endoscopy showed multiple strictures with ulcers in the small intestine. The capsule was found in proximal to one of the stenosis, and was removed by double-balloon enteroscopy. Based on endoscopic findings, NSAID-induced enteritis was diagnosed. Although anemia and hypoalbuminemia improved after discontinuing NSAID, the patient developed ileus and underwent partial resection of the ileum. Multiple diaphragm-like strictures were present in the resected intestine. The current case highlights the importance of screening for intestinal strictures when NSAID ulcer is suspected.

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**Key words:** Diaphragm disease, protein-losing enteropathy, non-steroidal anti-inflammatory drug (NSAIDs) induced enteritis, double-balloon enteroscopy

## Introduction

Capsule endoscopy emerged as a minimally invasive method to observe small intestine. However, although relatively rare, complications such as retention of capsule endoscopy and perforation can occur [1]. Non-steroidal anti-inflammatory drugs (NSAIDs) are the most commonly used anti-inflammatory, analgesic, and antipyretic medications that are particularly favored for the treatment of rheumatoid arthritis and other musculoskeletal disorders. Formation of gastric ulcer is a well-known side effect of NSAIDs administration [2]. Recent development of capsule endoscopy and double balloon enteroscopy also lead to increased report of NSAIDs-induced enteritis and ulcers in the small intestine [3,4]. This complication can result in intestinal bleeding,

anemia, protein losing syndrome. Notably, NSAIDs-induced intestinal ulcer can also induce a rare condition called diaphragm like stricture (or diaphragm disease), characterized by the presence of one or more thin septa that can narrow the intestinal lumen [4-6]. Diaphragm disease can cause symptoms such as abdominal pain and ileus [6,7]. Here we report a case of diaphragm disease with NSAIDs-induced ulcer which developed multiple severe strictures in ileum, subsequently causing retention of capsule endoscopy and ileus.

## Case Report

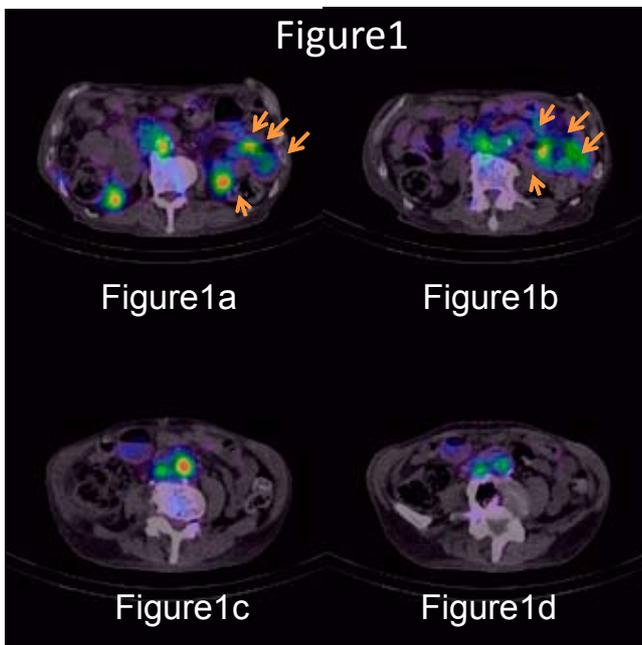
A 77-year-old man with rheumatoid arthritis was admitted to our hospital due to anemia, tarry stool, and hypo-albu-

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minemia (serum albumin; 1.9 g/dL). He had a history of heavy NSAIDs use for a few years. Esophagogastroduodenoscopy and total colonoscopy showed no abnormalities. The source of bleeding was not detected either by abdominal ultrasound or computed tomography (CT). Urinalysis was negative for proteinuria.  $^{99m}\text{Tc}$ -labeled human serum albumin scintigraphy indicated protein loss from small intestine (Figure 1a-1b). Capsule endoscopy showed multiple ileal strictures with active ulcers. Upon watchful follow up after the initiation of the examination, capsule endoscopy was not discharged for several days although the patient had no symptoms. Abdominal radiography examination confirmed retention of the capsule endoscope. Oral double-balloon enteroscopy was performed in an attempt to retrieve the capsule and to further examine the small intestine. Multiple annular ulcers with mild strictures and reddish mucosa were observed in the ileum. (Figure 2a-2c). Double-balloon endoscope managed to pass through a few strictures. The capsule was retained proximal to one of the stenosis and was removed using a net snare (Figure 2d). The patient was diagnosed as NSAIDs-induced ulcers after ruling out the other diseases such as malignant lymphoma and tuberculosis based on the intestinal endoscopic findings, serological tests, and pathological findings. Since location of the ulcers and  $^{99m}\text{Tc}$  scintigraphy activity were similar, it was considered that protein loss was due to NSAIDs ulcers and en-

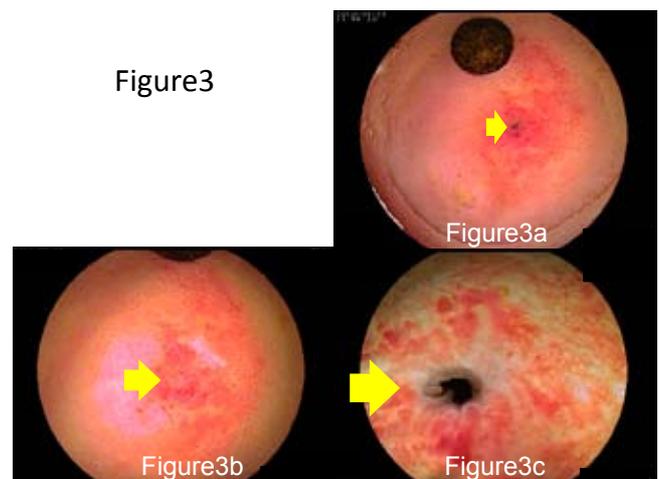


**Figure 1.**  $^{99m}\text{Tc}$  labeled human serum albumin scintigraphy showed high up-take of small intestine, indicating protein loss from small intestine (Figure 1a-1b), and after discontinuing NSAIDs, the high up-take disappeared. (Figure 1c-1d).



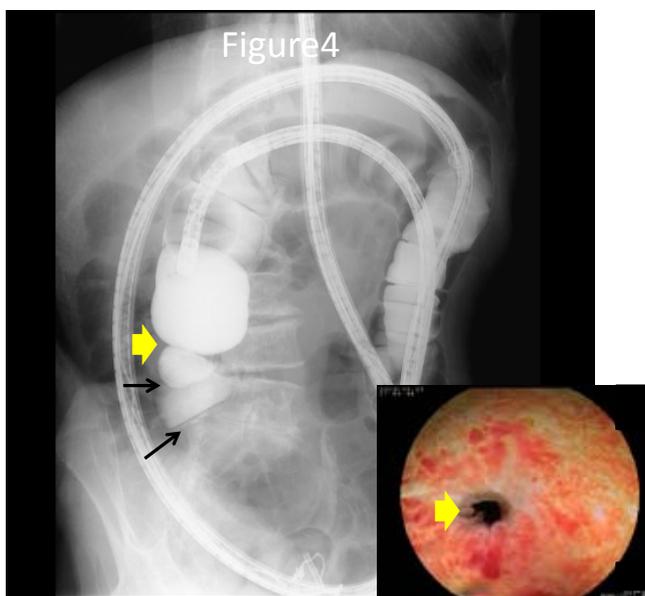
**Figure 2.** Double balloon enteroscopy showing multiple ulcers and mild strictures. (Figure 2a-2c). Double balloon endoscope managed to pass through a few strictures without endoscopic balloon dilation. The retained capsule endoscope was found proximal to one of the strictures, and was removed by net snare (Figure 2d).

teropathy. After the NSAIDs was discontinued and density liquid diet was started, anemia and hypo-albuminemia showed improvement. However, after 3 weeks, the patient complained nausea and vomiting. Abdominal radiography and CT showed ileus and obstruction of the small intestine, which was controlled by trans-nasal ileus tube. After the recovery from ileus symptoms, oral double-balloon enteroscopy was performed for the second time in order to observe the severity of strictures and in an attempt to perform balloon dilation. In the mid ileum, a severe stricture with a pin-hole opening was found (Figure 3a-3c). Radiography with contrast showed a few more short strictures at the anal side (Figure 4). Although ulcerations had improved, the

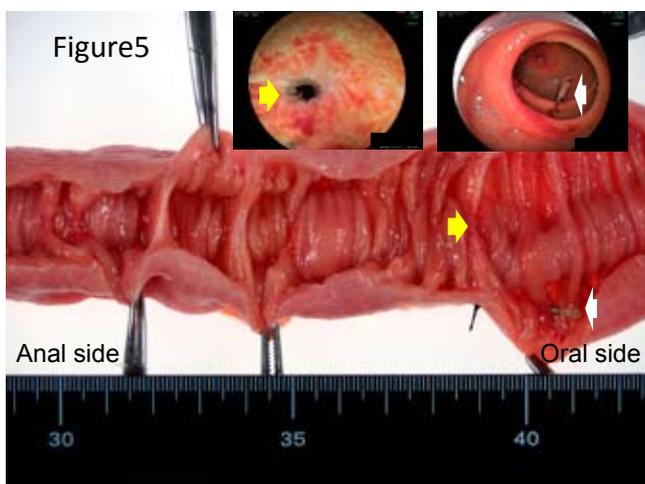


**Figure 3.** Upon the second double-balloon enteroscopy, the severe stricture with a pin-hole opening was observed (Figure 3a-3c, arrows).

strictures had become more severe than the lesions observed during the first double-balloon enteroscopy examination. It was evident that this condition could not be resolved by endoscopic procedures. Subsequently, the patient underwent the surgical partial resection of the ileum. One segment of small bowel measuring 39 cm in length was taken from the mid ileum. The resected intestine showed multiple stricture bands along the mucosal surface as seen in Figure 5. Pathological examination showed hypertrophy and fibrosis of the submucosal layer at the site of strictures, which was consistent with a diaphragm disease induced by NSAIDs therapy. Neither granuloma nor malignancy was observed. The patient has been free of symptoms after the surgery.



**Figure 4.** Radiography with contrast administration upon double balloon enteroscopy showed diaphragm-like strictures (arrows). Thick arrow indicates the pin-hole stricture that was observed by double balloon enteroscopy.



**Figure 5.** Surgical resection of the ileum proved multiple stricture bands along the mucosal surface (yellow arrows), and the marking was clipped just at the oral side of pin-hole stricture (white arrows).

## Discussion

The current case showed NSAIDs-induced annular ulcers and concentric stenosis, which caused an incidental retention of capsule endoscopy. Diaphragm disease is a relatively rare small-intestinal lesion associated with NSAIDs which was first reported in 1980s [5]. Diaphragm strictures are usually formed by multiple thin, concentric, 2- to 4-mm thick diaphragm like septa in the small intestine [5,8]. Recently, double-balloon enteroscopy and capsule endoscopy emerged as newly developed tools that allow the direct examination of NSAIDs ulcers, which lead to increased reports demonstrating endoscopic images of NSAIDs-induced enteritis including several cases of diaphragm strictures [4,7,9-11]. Decrease in prostaglandin (PG) production is considered to be the main cause of small bowel injuries due to NSAIDs [9,10]. NSAIDs are thought to inhibit mucosal PG synthesis by inhibiting COX-1 activity, which is pivotal in maintaining homeostasis of intestinal mucosa. Pathological findings of diaphragm disease are fibrosis in the submucosal and thickening of the mucosa, while the proper muscle layer is usually intact [9]. Clinical presentation of diaphragm disease is nonspecific and may include gastrointestinal obstructive symptoms, anemia, or abdominal pain [1]. Of note, in this patient, double-balloon enteroscopy might have shown relatively active and healing phase of endoscopic findings of NSAIDs enteropathy. In active phase, double-balloon enteroscopy showed multiple active ulcers and reddish edematous mucosa in the ileum with protein losing enteropathy, but the stenosis was mild and double-balloon enteroscopy scope could pass through the lesions. On the other hand, in healing phase, the mucosal inflammation and protein losing enteropathy had improved but the stenosis became more severe. Retention of the capsule endoscope occurs in approximately 0.75% of capsule endoscopy examinations [12]. While incidents of capsule retention are known to be as high as 13% in Crohn's disease, it is generally less recognized that the NSAIDs ulcer can also induce such condition [13]. Most of the current guidelines propose performing radiography to identify stenosis if Crohn's disease is a known or suspected diagnosis, especially when patients have obstructive symptoms or abdominal pain. Notably, stenosis induced by NSAIDs ulcers can be challenging to diagnose by radiography as the stricture is short and show pseudo-fold patterns. Indeed, study by Matsumoto *et al.* showed that radiography was able to depict small mucosal defects in only 17% of the patients that had stenosis induced by NSAIDs [7]. A newly developed "patency capsule", a self-dissolving capsule mimicking capsule endoscopy, is shown to be an useful tool for estimating stenosis prior to capsule endoscopy [14]. Since combination of radi-

ography and patency capsule is shown to demonstrate high sensitivity (100%) for intestinal stenosis, these methods may be beneficial to exclude the presence of a significant stricture in NSAID patients [14].

The current case also presented with protein losing enteropathy. Previous studies demonstrated that about 75% of patients receiving long term NSAIDs develop inflammation in the small intestine, while they rarely result in protein losing enteropathy [5]. It is reported that intestinal permeability may contribute to NSAIDs enteropathy [15]. For example, patients with rheumatoid arthritis who had not received NSAIDs had entirely normal permeability, whereas the patients with treated with NSAIDs had small bowel inflammation and increased intestinal permeability. In a small study, patients on NSAIDs were studied simultaneously with <sup>111</sup>indium leukocytes and <sup>55</sup>chromium labeled proteins to assess intestinal inflammation and protein loss, respectively. All those with NSAIDs induced-enteropathy had protein-losing enteropathy [16]. Therefore, there might be a high frequency of latent protein loss in the patients with NSAIDs use.

Primary treatment for NSAIDs-induced injury is discontinuation of the NSAIDs. Clinically, proton pump inhibitors (PPIs) are the one of the main drugs for the prevention of NSAIDs-induced ulcers. Other medications, such as rebamipide and misoprostol, are reported to inhibit intestinal mucosa injuries [17,18]. In this case, we discontinued NSAIDs and started PPI and misoprostol, which lead to improvement of the ulcers.

In conclusion, NSAIDs ulcers in small intestine can cause various conditions including hemorrhage, protein losing enteritis, and more importantly, stenosis. The current case highlights the importance of screening for intestinal strictures when NSAIDs ulcer is suspected.

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