

## Case Report

# A case of multiple small intestinal ulcers associated with rheumatoid arthritis in a patient who underwent small intestinal resection twice

Yoshihisa MORISAKI<sup>1</sup>, Shoichiro SUZUKI<sup>1</sup> and Kazuo HASE<sup>1</sup>

*J. Natl. Def. Med. Coll.* (2026) 51 (3) : 90 – 97

**Abstract:** The patient was a woman in her 70s undergoing treatment for rheumatoid arthritis (RA). She underwent a small intestinal resection owing to recurrent intestinal obstruction. Four years later, the obstruction recurred, necessitating another small bowel resection. Histopathologic examination of both resected specimens revealed multiple shallow ulcers in the ileum. These findings were consistent with non-specific small intestinal ulcers, with no evidence of vasculitis or amyloidosis. Macroscopic observations suggested non-steroidal anti-inflammatory drug (NSAID)-induced small intestinal ulcers; however, the patient had no history of NSAID use prior to her first surgery. Consequently, the adverse effects of various RA medications were considered the primary cause of the ulcers. This report presents a clinical and pathologic examination of the case, alongside a discussion of the implications related to the patient's RA treatment.

**Key words:** multiple small intestinal ulcers / rheumatoid arthritis

## Background

Rheumatoid arthritis (RA) is a systemic inflammatory disease of unknown etiology characterized by chronic arthritis<sup>1)</sup>. RA is associated with a range of gastrointestinal complications, which may arise from secondary amyloidosis, as well as from therapeutic interventions, such as the administration of non-steroidal anti-inflammatory drugs (NSAIDs)<sup>1)</sup>. In this report, we present a case of RA in which the patient underwent two small intestinal resections owing to intestinal obstruction. Histopathologic examination of resected specimens during both surgeries revealed multiple nonspecific small intestinal ulcers, with no evidence of vasculitis or amyloidosis. We aimed to elucidate the etiology of these lesions by analyzing the clinical course and medical history of the patient.

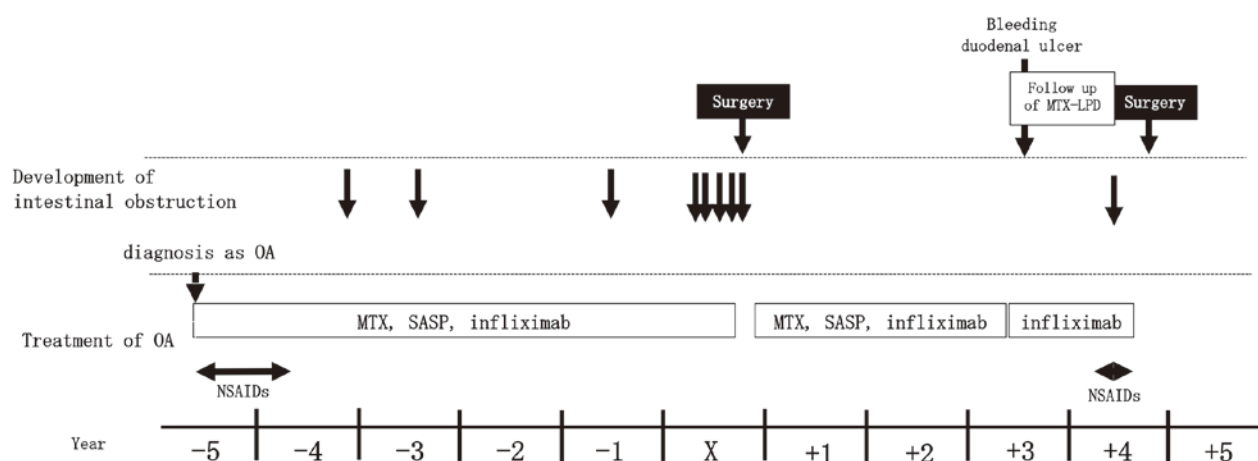
## Case presentation

A woman in her 70s presented to our hospital in October of the year X with abdominal pain and vomiting. She was diagnosed with intestinal obstruction and subsequently admitted for treatment. Upon admission, tenderness was noted primarily in the lower abdomen; however, no muscle guarding was observed. Blood tests indicated a mildly elevated C-reactive protein level of 0.71 mg/dl, while her complete blood count and biochemical tests showed no abnormalities. Abdominal computed tomography revealed focal small bowel dilatation in the right lower abdomen, but no findings indicative of strangulated intestinal obstruction. Given her history of three laparotomies, adhesive intestinal obstruction was diagnosed. Past medical history revealed an appendectomy performed 61 years ago, a bilateral salpingo-oophorectomy owing to ectopic pregnancy 33 years ago, and a hysterectomy

<sup>1</sup>Tokorozawa Mihara General Hospital, Tokorozawa, Saitama 359-0045, Japan

Received February 17, 2026  
Accepted May 1, 2026

Table 1. Clinical course



NSAIDs: non-steroidal anti-inflammatory drugs; MTX: methotrexate; SASP: salazosulfapyridine

for uterine fibroids 31 years ago. Over the past 4 years, she has been hospitalized at our facility seven times for intestinal obstruction, during which she received conservative treatment (Table 1).

Additionally, she has a diagnosis of RA and has been treated primarily with methotrexate (MTX), salazosulfapyridine (SASP) and infliximab, a tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) inhibitor, since year X-5. NSAIDs were administered only during the first 10 months of her treatment (Table 1).

The patient had been experiencing recurrent intestinal obstruction for the past 4 years with this being the eighth occurrence. The initial surgical approach utilized laparoscopy; however, the site of obstruction could not be visually identified, necessitating a switch to laparotomy.

A midline incision in the lower abdomen was performed, revealing three strictures in the ileum. Approximately 36 cm of small intestine, encompassing all palpated strictures, was resected and reconstructed using functional end-to-end anastomosis (FEEA). The resected specimen exhibited a total of seven ulcerative lesions and ulcer scars (Fig. 1). The most distal narrowed area was obstructed by food residue (Fig. 1). Histopathologic examination indicated a UI-II ulcer, with no specific findings such as

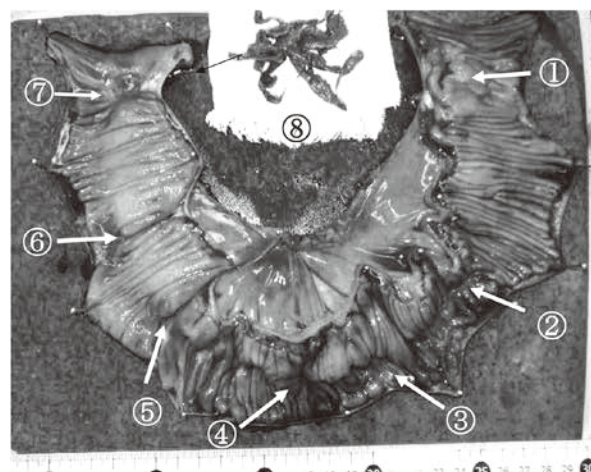


Fig. 1 Resected specimen from initial surgery

A total of seven ulcerative lesions of varying stages were observed (white arrows): (1) A2 stage; (2) H1 stage; (3,4,7) S1 stage; (5,6) annular ulcer; and (8) Food residue accumulated in the intestine at the anal end.

epithelioid granulomas, caseous necrosis, or vasculitis, or amyloid deposition (Fig. 2). Apoptotic bodies were found scattered within the epithelium at the edge of the ulcer and deep in the crypts of the intervening mucosa (Fig. 3). Macroscopic and histopathologic findings suggested nonspecific multiple ulcers of the small intestine<sup>2)</sup>, simple ulcers<sup>3)</sup>, and NSAID-induced small intestinal ulcers<sup>4)</sup>. The primary symptoms of nonspecific multiple small intestinal ulcers, such as long-term iron deficiency anemia and hypoproteinemia<sup>2)</sup>, were absent, leading to the

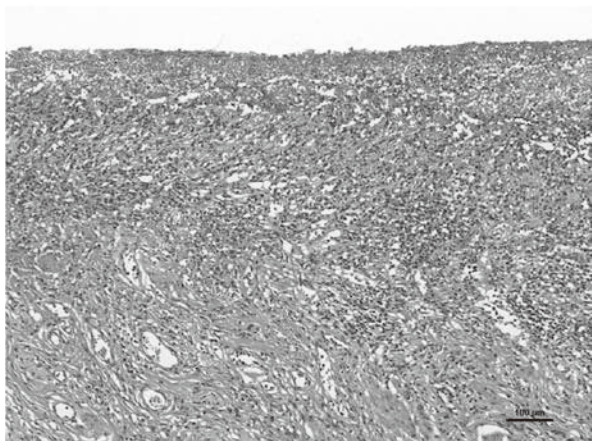


Fig. 2 Histopathologic finding of ulcer  
Fibrosis was observed in the UI-II ulcer and the ulcer base, but no specific findings such as epithelioid cell granuloma, central caseous necrosis, or vasculitis were observed.

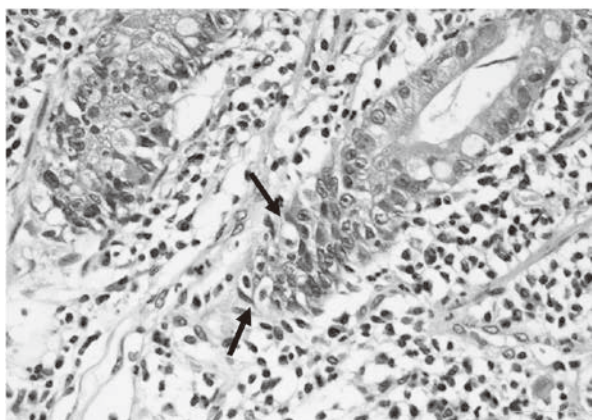


Fig. 3 Histopathologic finding of ulcer  
Fibrosis was observed in the UI-II ulcer and the ulcer base, but no specific findings such as epithelioid cell granuloma, central caseous necrosis, or vasculitis were observed.

exclusion of this diagnosis. Additionally, as the patient had not ingested NSAIDs for four years, NSAID-induced small intestinal ulcers were also ruled out, ultimately resulting in a diagnosis of simple ulcer. The patient's recovery was favorable, and she was discharged on the seventh day of hospitalization. RA treatment with MTX, SASP, and infliximab continued at Clinic A. In May of X + 3 year, enlargement of the axillary and left cervical lymph nodes was observed. A cervical lymph node biopsy confirmed angioimmunoblastic T-cell lymphoma, leading to a definitive diagnosis of MTX-associated lymphoproliferative disorder<sup>5)</sup>.

Consequently, MTX and infliximab were discontinued, while RA treatment transitioned to iguratimod. In May of the same year, the patient developed melena and was urgently admitted to Hospital B, where a bleeding duodenal ulcer was diagnosed, and endoscopic hemostasis was performed using coagulation and clipping techniques. By May of the following year, the lymph node enlargement had resolved. DCFS was resumed at Clinic A in July of X + 4 year, but abdominal pain recurred 1 month later, necessitating readmission to Hospital B. Gastroscopy revealed scarring from the previously observed duodenal ulcer, along with multiple new S2-stage ulcers in the stomach. Colonoscopy identified four erosive lesions from the terminal ileum to the splenic flexure, culminating in a diagnosis of NSAID-associated enteropathy. The patient's condition improved following the discontinuation of DCFS, and she was discharged in August of X + 4 year. In September of the same year, the patient was readmitted to Hospital B owing to intestinal obstruction. Conservative treatment was initially effective; however, the obstruction recurred upon dietary reintroduction. An ileus tube was inserted, and small-bowel examination indicated ileal stenosis (Fig. 4). The patient was referred to our hospital for surgery in December of the fourth year. During laparotomy, the tip of the ileus tube was palpated approximately 60 cm from the ileocecal junction. Although no hard mass was detected, the ileus tube could not be advanced toward the anal side, indicating a stricture at this site. Approximately 10 cm of the ileum, including the stricture site, was resected, and reconstruction with FEEA was attempted. Upon meticulous palpation of the surrounding ileum, significant hardening was noted at the anastomosis site from the previous surgery, leading to an additional resection of approximately 20 cm of ileum, including the prior anastomosis site, which was then reconstructed using FEEA. The patient was discharged 39 days post-

surgery. Histopathologic examination of the initially resected 10 cm of ileum revealed no mucosal lesions on the surface, but significant wall thickening owing to edema was observed (Fig. 5). Further histologic analysis identified small ulcerative lesions in four locations beneath the regenerated mucosal epithelium, accompanied by substantial surrounding edema (Fig. 6). It was postulated that the obstruction resulted

from considerable submucosal edema. Additionally, three S1 or S2 stage ulcers were found in the resected distal ileum. Histopathologic examination indicated nonspecific inflammation in all ulcers, similar to those in the initial surgical specimen. No apoptotic bodies were detected. The patient, who had a history of taking DCFS, demonstrated improvement following their discontinuation and was ultimately diagnosed with NSAID-induced small intestinal ulcers. Currently, 13 months post-surgery, the patient is under follow-up at Clinic A and is good health

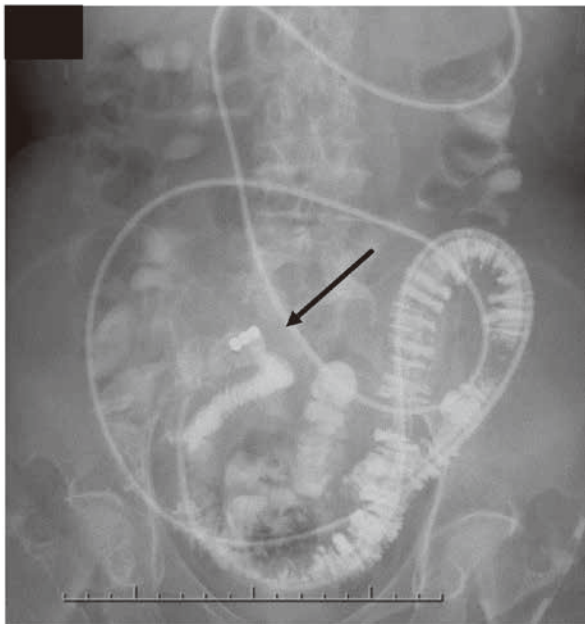


Fig. 4 Small-bowel examination via an ileus tube  
Small-bowel stenosis is observed on the anal side of the tip of the ileus tube (black arrow).

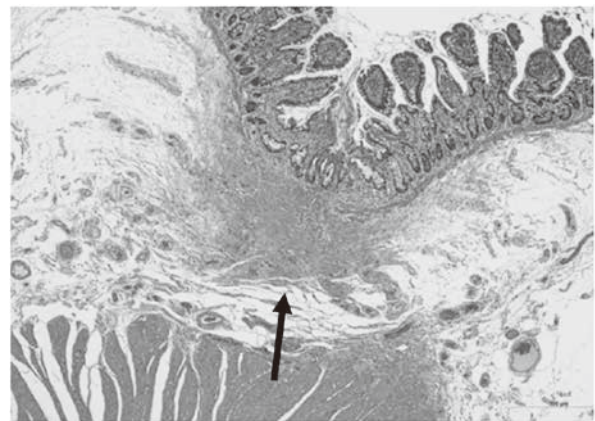


Fig. 6 Pathologic findings of the proximal ileum at the second surgery

A small ulcerative lesion (black arrow), accompanied by significant surrounding edema, was observed beneath the regenerated mucosal epithelium.

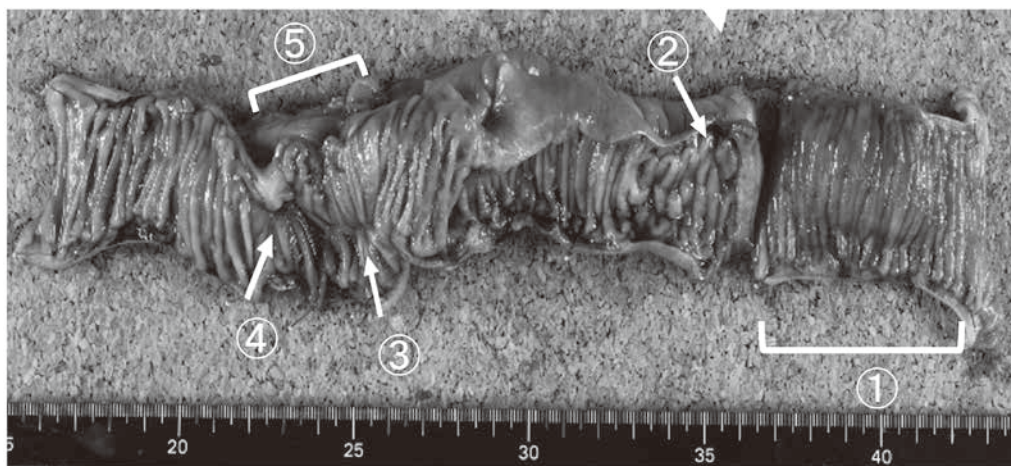


Fig. 5 Resected specimen from the second surgery

- (1) The initially resected ileal specimen revealed no mucosal lesions on the mucosal surface, but edematous wall thickening was observed.
- (2) S2 ulcer. (3,4) S1 ulcer. (5) Anastomosis at initial surgery

with no signs of recurrence.

## Discussion

RA is associated with various gastrointestinal complications, including those arising from secondary amyloidosis and therapeutic agents such as NSAIDs<sup>1)</sup>. A study by Allison et al.<sup>6)</sup> in 1992 revealed that the incidence of small intestinal ulcers in 713 autopsy cases was 0.6% in patients not using NSAIDs, while it significantly increased to 8.4% in those who were taking NSAIDs. Since then, NSAID-induced small intestinal ulcers have been recognized as noteworthy gastrointestinal complication in RA. Since 2000, advancements such as capsule endoscopy (CE) and double balloon endoscopy (DBE) have emerged, facilitating significant progress in diagnosis small intestinal disorders<sup>4)</sup>. Beginning around 2005, studies utilizing CE have primarily been conducted in Europe and the United States, focusing on healthy volunteers, and have demonstrated considerable mucosal damage in the small intestine owing to NSAIDs<sup>7)</sup>. In Japan, investigations employing CE and DBE have similarly indicated a high prevalence of mucosal damage in patients using NSAIDs<sup>7,8)</sup>. Consequently, cases of NSAID-related small intestinal ulcers have been accumulating, with their clinicopathologic characteristics becoming increasingly well understood<sup>4,7,9,10)</sup>.

NSAID-induced small intestinal ulcers are characterized by several distinct features: (1) a range of macroscopic morphologies, including relatively shallow round or nearly round ulcers, irregular ulcers, punched-out ulcers, annular ulcers, ulcer scars, and membranous strictures, often presenting as shallow, well-defined ulcers; (2) the presence of various ulcerative lesions simultaneously within the same patient, with multiple small ulcers being common; (3) membranous strictures potentially present throughout a broad section of the small intestine (unlike most ulcers that are typically located in the ileum); and (4) a high frequency of apoptotic

bodies is observed histopathologically. In our case, specimens resected during two surgeries exhibited multiple ileal ulcers, with histopathologic findings consistent with nonspecific small intestinal ulcers. The first surgery revealed near-round and annular ulcers ranging from A2 to H1 stage, while the second surgery identified S1 stage ulcers, all of which were shallow and up to UL-II stage. These findings align with the characteristics of NSAID-induced small intestinal ulcers.

In diagnosing NSAID-induced small intestinal damage, it is crucial consider morphological characteristics alongside the patient's history of NSAID use, the exclusion of other drug-induced enterocolitis<sup>10)</sup>. At the time of the first surgery, the patient had been taking NSAIDs for approximately 10 months during the early stages of RA treatment but had not used them 4 years and 2 months prior to the surgery. Although apoptotic bodies were identified pathologically, this finding was unlikely to indicate an NSAID-induced small intestinal ulcer, leading to a final diagnosis of a simple ulcer. Simple ulcers have also been documented in cases where small intestinal resection was performed owing to intestinal obstruction, similar to our case<sup>3,11,12)</sup>. These ulcers are characterized by deep, well-defined, round or oval ulcers with a punched-out appearance, often occurring at or near the ileocecal valve<sup>12)</sup>. Some simple ulcers, including ours, are classified as UL-I or II<sup>3)</sup>. Moreover, these ulcers exhibit a high recurrence rate, typically reappearing in the ileum close to the anastomosis<sup>3)</sup>. These characteristics are consistent with our case and support a diagnosis of a simple ulcer.

At the time of the second surgery, the patient had been prescribed DCFS 1 month before the onset of abdominal pain, which resolved following the discontinuation of DCFS. Therefore, the multiple small intestinal ulcers observed during the second surgery were clinically regarded as typical NSAID-induced

small intestinal ulcers. However, it is unlikely that simple small intestinal ulcers and NSAID-induced ulcers would manifest asynchronously in the same patient. Ikeda et al.<sup>13)</sup> emphasize that non-neoplastic small intestinal ulcers necessitate consideration of disease progression and treatment-related changes, underscoring the importance of a comprehensive assessment based on clinical information. Furthermore, in a report discussing a case of obstructive ileus owing to simple small intestinal ulcers associated with RA. Tanaka et al.<sup>11)</sup> noted that the patient was taking oral steroids and MTX, and that numerous oral medications were utilized during the RA treatment process, complicating the identification of the causative drug, they acknowledged the potential for a drug-related cause.

The presence of apoptotic bodies in the specimen from the first surgical procedure in our case is a common finding in NSAID-induced small intestinal ulcers<sup>10)</sup>. However, this observation is not exclusive to NSAIDs and is considered significant in the context of drug-related gastrointestinal diseases<sup>14)</sup>. Prior to the first surgery, our patient was being treated with SASP and MTX, and iguratimod was administered in conjunction with DCFS before the second surgery. Based on this information, it is reasonable to conclude that the second surgical specimen was not exclusively related to NSAIDs and that both surgical specimens represented drug-induced small intestinal ulcers.

Regarding drug-induced small intestinal ulcers in RA patients, recent CE studies have indicated that antirheumatic medications, such as MTX, disease-modifying antirheumatic drugs (DMARDs), and low-dose corticosteroids, can lead to small intestinal injury<sup>8)</sup>. Furthermore, it is believed that the concurrent use of NSAIDs in patients receiving DMARDs increases the incidence of bowel injury<sup>15)</sup>. Conversely, NSAID-induced injury appears to be mild in RA patients undergoing anti-TNF- $\alpha$  antibody therapy<sup>7, 15)</sup>.

Given these findings, we hypothesize that DMARDs were the primary contributors to the multiple small intestinal ulcers observed in our case, with NSAIDs exacerbating the injury upon re-exposure; however, the condition improved following discontinuation of the offending drug. Moreover, we suggest that anti-TNF- $\alpha$  treatment may have been played in a complex role in this scenario. Tabuchi et al.<sup>16)</sup> conducted a comparative analysis of the frequency and severity of gastrointestinal disorders induced by NSAIDs between RA in patients with RA versus osteoarthritis (OA), receiving a significantly higher prevalence and severity of intestinal disease in RA patients, which implies a potential influence of immunopathology in RA. The patient in our case had visited the hospital five times over 8 years owing to abdominal pain prior to her RA diagnosis. Initially diagnosed with acute enteritis, but we posit that there may have been pre-existing small intestinal damage attributable to immune abnormalities associated with the onset of RA, which may have been subsequently mitigated by various RA treatments. Furthermore, Makino et al.<sup>17)</sup> reported a surgical case of small intestinal perforation during MTX treatment for RA, documenting the presence of Epstein-Barr virus (EBV) in a longitudinal ileal ulcer, alongside elevated EBV antibody titers. This underscores the need for further investigation into the etiology of small intestinal linked to RA, particularly regarding the involvement of EBV.

The primary strategy for preventing and managing drug-induced small intestinal injury is to continue to potentially causative medication. It is widely recognized that NSAID-induced small intestinal ulcers typically heal swiftly upon cessation NSAIDs<sup>18)</sup>. However, discontinuing such medications can be challenging owing to the necessity of managing the underlying disease, particularly in the context of RA. Currently, there is no established pharmacologic treatment for NSAID or low-dose aspirin-induced small intestinal damage<sup>18)</sup>. Nevertheless, recent

clinical trials have confirmed the efficacy of rebamipide, misoprostol, and probiotics in clinical trials using CE<sup>7)</sup>. Furthermore, balloon dilation for benign small intestinal strictures has been developed and it has shown significant utility in addressing strictures caused by NSAIDs<sup>4)</sup>. In cases of intestinal obstruction attributable to strictures associated with DMARDs or NSAIDs administration, as in the present case, balloon dilation may potentially serve as a non-surgical alternative.

## Conclusion

We report a case of multiple small intestinal ulcers associated with RA, which necessitated two small intestinal resections. When gastrointestinal symptoms arise during RA treatment, a comprehensive examination of the gastrointestinal tract, including the small intestine, using CE and DBE is essential for appropriate treatment.

## Conflict of interest

The authors declare no conflict of interest associated with this manuscript.

## Acknowledgements

We would like to thank Honyaku Center Inc. for English Language editing.

## References

- 1) Kobayashi H, Fuchigami T.: Gastrointestinal lesions in rheumatoid arthritis. *Stomach and Intestine*. (TOKYO) 38: 521-528, 2003.
- 2) Yokoyama K, Harada Y, Kanazawa J, et al.: Chronic enteropathy associated with SLCO2A1 gene (CEAS). *Endosc. Digest*. 37: 797-802, 2025.
- 3) Shimazaki J, Watanabe Y, Nagata T, et al.: A case of ileus due to a small intestinal simple ulcer treated with laparoscopic surgery. *J Abdom Emerg Med*. 30: 505-508, 2010.
- 4) Ishihara M, Ohmiya N, Goto H.: The trend view of nonsteroidal anti-inflammatory drug-induced small bowel injury. *Jpn J gastroenterol*. 107: 1905-1909, 2010.
- 5) Murakami H, Makita M, Ishikawa T, et al.: Angioimmunoblastic T-cell lymphoma presenting as a methotrexate-associated lymphoproliferative disorder with extreme peripheral blood plasmacytosis. *Intern Med*. 61: 2655-2660, 2022.
- 6) Allison MC, Howatson AG, Torrance CJ, et al.: Gastrointestinal damage associated with the use of nonsteroidal anti-inflammatory drugs. *N Engl J Med*. 327: 749-754, 1992.
- 7) Otani K, Watanabe T, Fujiwara Y.: Present issues and measures for NSAID-induced small intestinal damage. *Clin Rheumatol*. 29: 77-84, 2017.
- 8) Sugimori S, Watanabe T, Tabuchi M, et al.: Evaluation of small bowel injury in patients with rheumatoid arthritis by capsule endoscopy: effects of anti-rheumatoid arthritis drugs. *Digestion*. 78: 208-213, 2008.
- 9) Matsumoto T, Kudo T, Esaki M, et al.: Prevalence of non-steroidal anti-inflammatory drug-induced enteropathy determined by double-balloon endoscopy: a Japanese multicenter study. *Scand J Gastroenterol*. 43: 490-496, 2008.
- 10) Nagasue T, Kawasaki K, Torisu T.: NSAIDs-induced ulcer. *Stomach and Intestine*. (TOKYO) 59: 1810-1811, 2024.
- 11) Tanaka H, Teranishi S, Hiramatsu K, et al.: A case of small bowel obstruction associated with simple ulcer managed by emergency operation. *J Abdom Emerg Med*. 33: 731-734, 2013.
- 12) Wada Y, Shioya T, Kuroda S, et al.: A case of ileus due to a simple ulcer of the small intestine treated with laparoscopy-assisted surgery. *J Jpn Coll Surg*. 40: 1113-1119, 2015.
- 13) Ikeda K, Iwashita A, Tanabe H, et al.: Pathological diagnosis of small intestinal ulcers; Discrimination of non-neoplastic lesions. *Stomach and Intestine*. (TOKYO) 49: 1258-1266, 2014.
- 14) Yao T, Okano S, Takeda T, et al.: Histopathological features of drug-related digestive diseases. *Stomach and Intestine*. (TOKYO) 55: 883-889, 2020.
- 15) Watanabe T, Tanigawa T, Shiba M, et al.: Anti-tumor necrosis factors agents reduce non-steroidal anti-inflammatory drugs-induced small bowel injury in rheumatoid arthritis patients. *Gut*. 63: 409-414, 2014.
- 16) Tacheci I, Bradna P, Douda T, et al.: Small intestinal injury in NSAID users suffering from rheumatoid arthritis or osteoarthritis. *Rheumatol Int*. 36: 1557-1561, 2016.
- 17) Makino Y, Tani C, Miyokawa N, et al.: Multiple Intestinal Ulcers Associated with Primary Epstein-Barr Virus Infection in a Patient with Rheumatoid Arthritis Undergoing Methotrexate Therapy. *Inter Med*. 54: 2851-2855, 2015.
- 18) Nisimura N, Yamamoto H, Sunada K, et al.: Treatment for NSAID-induced small bowel injuries. *Stomach and Intestine*. (TOKYO) 46: 166-172, 2011.

## 2 回の小腸切除を施行した慢性関節リウマチに併発した多発性小腸潰瘍の 1 例

森崎善久<sup>1</sup>，鈴木昭一郎<sup>1</sup>，長谷和生<sup>1</sup>

防医大誌 (2026) 51 (3) : 90 – 97

**要旨：**症例は，慢性関節リウマチ（rheumatoid arthritis: RA）で治療中の71歳，女性。反復する腸閉塞のため小腸切除術を施行した。4年後に腸閉塞が再燃し再び小腸切除を施行した。切除標本ではともに回腸に深達度の浅い多発性の潰瘍を認めた。病理組織学的には血管炎やアミロイドーシスを伴わない多発性の非特異性小腸潰瘍であり，肉眼的にNSAIDs起因性小腸潰瘍に矛盾しない所見であった。しかし，1回目の手術前にはNSAIDsの内服歴がなく，最終的には複数のRA治療薬による影響が主たる要因と考えられた。RAの治療経過とともに臨床病理学的に検討し，発生要因について考察を加えて報告する。

**索引用語：** 多発性小腸潰瘍      ／      慢性関節リウマチ

---

<sup>1</sup> 所沢美原総合病院