

# Non-steroidal anti-inflammatory drug-induced enteropathy as a major risk factor for small bowel bleeding

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# Abstract

**Background:** Small bowel (SB) bleeding accounts for 5% of all gastrointestinal (GI) bleeding cases and 80% of obscure GI bleeding cases. Although angioectasia is the common etiology of SB bleeding, nonsteroidal anti-inflammatory drug (NSAID)-induced SB lesions are also reported as a major cause in studies from Eastern countries. Herein, we assessed the frequency of occurrence of NSAID-induced SB lesions in Korean patients with obscure GI bleeding.

**Methods:** We retrospectively analyzed medical records of all consecutive patients aged  $\geq 18$  years that underwent capsule endoscopy from March 2018 to February 2019 at Ulsan University Hospital and Kosin University Gospel Hospital.

**Results:** Of the 83 subjects (all were Korean; mean age  $\pm$  standard deviation:  $59 \pm 18$  years; age range: 18–84 years; men:  $n=52$ ; women:  $n=31$ ), 55 (66.2%) had stools with clear blood and 28 (33.8%) had normal stools with iron deficiency anemia. The detection rate of SB bleeding and lesions using capsule endoscopy was 72.3% (60 of 83 patients). A significantly higher frequency (40 of 51) of ulcerative/erosive lesions than other causes was observed in patients with inactive bleeding but visible SB lesions. As a result, NSAID-induced enteropathy accounted for 41.7% (25 of 60) of all SB bleeding cases.

**Conclusions:** Contrary to what is reported for patients in Western countries, this study in Korean patients showed an improved diagnostic yield of capsule endoscopy for obscure GI bleeding and that NSAID-induced enteropathy was the most common etiology of SB bleeding. Aggressive small intestine examination is required for patients with unexplained GI bleeding.

## Background

Obscure gastrointestinal (GI) bleeding is defined as persistent or recurrent bleeding of unknown origin despite repetitive diagnostic testing, including upper GI endoscopy and colonoscopy.<sup>1</sup> Small bowel (SB) bleeding accounts for 80% of obscure GI bleeding cases and 5% of all GI bleeding cases. Unexplained iron deficiency anemia manifests in 30–40% of obscure GI bleeding cases.<sup>2</sup> Capsule endoscopy is the first-line examination in cases of obscure GI bleeding and the third diagnostic test after negative upper and lower endoscopy results in cases of ongoing overt bleeding.<sup>3–6</sup> Whereas angioectasia is the most common etiology of SB bleeding in Western countries,<sup>4,7,8</sup> nonsteroidal anti-inflammatory drug (NSAID)-induced SB lesions are the major cause reported in Japanese studies.<sup>9,10</sup>

NSAIDs are widely prescribed in most clinical conditions, yet it is well known that these drugs cause GI complications.<sup>11</sup> Although various studies have reported an association between NSAID intake and GI adverse effects,<sup>12,13</sup> the role of NSAIDs in SB bleeding remains to be elucidated. Therefore, we aimed to assess the frequency of NSAID-induced SB lesions in Korean patients with obscure GI bleeding who underwent capsule endoscopy.

# Methods

## Study population

We retrospectively evaluated medical records of all consecutive patients aged  $\geq 18$  years with obscure GI bleeding who underwent capsule endoscopy from March 2018 to February 2019 at Ulsan University Hospital and Kosin University Gospel Hospital. The indication for the test included bloody stool in patients with an unidentified source of bleeding and lesions during diagnostic evaluations, including upper GI endoscopy, colonoscopy, and abdominal computed tomography (CT) in the last 3 months.<sup>5</sup> We also included patients who had no visible bloody stool, showed persistent or repeated exacerbation of iron deficiency anemia despite iron supplement for  $>6$  months, and no hemorrhagic lesions identified during the above screening methods in the last 3 months.<sup>14</sup> Rebleeding was defined as recurrent anemia ( $\geq 2$  g/dL decrease in hemoglobin level), overt melena/ hematochezia or occult GI bleeding during the follow-up period.<sup>15</sup> This study was approved by the Institutional Review Boards (IRB of the Ulsan University Hospital (IRB No. 2019-10-014) and the Kosin University Gospel Hospital (IRB No. 2019-10-001)). The requirement for informed consent from patients was waived because patient records and information were de-identified prior to analysis.

## Capsule endoscopy

Capsule endoscopy was performed using Pillcam<sup>®</sup> (SB3, Given Imaging Ltd., Yoqneam, Israel) and MiroCam<sup>®</sup> (MC1200, IntroMedic Ltd., Seoul, Korea) devices. Given that both pieces of equipment have 12 hours of battery life, all endoscopies were performed for 12 hours. All patients fasted for 12 hours and received 40 mg of oral simethicone before the procedure to prevent air bubbles from forming.<sup>16</sup> Moreover, we used 2 L polyethylene glycol solution at least 2–16 hours before examination to improve the quality of the SB image.<sup>17,18</sup> Patients with bloody stool were examined in the hospital in all cases, and those who were referred due to anemia had an outpatient examination if there was no bloody stool. To prevent capsule retention, we checked the presence of small bowel stenosis in CT scan before capsule endoscopy. Five gastroenterologists with extensive experience in GI endoscopy reviewed and extensively discussed all capsule video images to reach a diagnosis. An erosion was defined as a roundish area of mucosal disruption smaller than the diameter equivalent to 1 circular fold of mucosa (also called the valves of Kerckring, valvulae conniventes or plicae circulares).<sup>19</sup> An ulcerative lesion was defined as a mucosal penetration with a diameter larger than 1 circular fold of mucosa.<sup>15</sup> The etiology of ulcerated lesions was determined based on clinical information and endoscopic findings. We examined NSAID-induced enteropathy based on the following criteria: history of NSAID use within the previous 1 month; endoscopic findings, including ulcers, erosions, scar changes, or luminal stenosis; improvement of clinical course and/or endoscopic findings after cessation of NSAID use; and exclusion of other etiologies, including infection, inflammatory bowel disease, or malignancy.<sup>12,20,21</sup> There is no criterion regarding the duration of NSAID use to diagnose NSAID-induced enteropathy. However, because SB injuries were

observed in 68% of healthy volunteers taking NSAIDs for only 1-2 weeks,<sup>20, 22</sup> we chose to include patients who had history of NSAID use within the previous 1 month as was done in a previous study.<sup>21</sup>

## Statistical analysis

Continuous variables were compared using Student's *t*-test and categorical variables were analyzed with chi-square or Fisher's exact test. A two-tailed *p*-value <0.05 was considered statistically significant. All statistical analyses were performed using the SPSS statistical package for Windows, Version 24.0 (SPSS Inc., Chicago, IL, USA).

# Results

## Sample analysis

We assessed 83 subjects (52 men and 31 women) who underwent capsule endoscopy during the study period (see Table 1 for patient characteristics). The subjects were Korean and aged 18–84 years (mean ± standard deviation: 59 ± 18 years). Of these, 55 (66.2%) patients had a clear bloody stool and 28 (33.8%) had a normal stool, all with iron deficiency anemia (Figure 1). The mean small bowel transit time was 6.39 hours (range 2.42-11.38 hours). Capsule retention was not occurred in this study. Most of patients (92.4%) showed score 3 or 2 of Boston bowel preparation scale.<sup>23</sup> A total of 37 patients had a history of taking NSAIDs/low-dose aspirin (Table 2). The brand name and dosage of NSAIDs were not clearly identified in the medical records. Musculoskeletal disorders were the most common indication for taking NSAIDs, while coronary artery disease and other cardiovascular diseases were the main indications for taking aspirin. The duration of NSAID use varied from 2 weeks to 10 years prior to the capsule endoscopy. An association with SB bleeding was considered only when NSAIDs/low-dose aspirin was taken within the previous 1 month. Of the 37 patients, 33 had SB lesions, of these, 25 patients were diagnosed with NSAID-induced enteropathy without other cause of SB bleeding. The main treatments for NSAID-induced enteropathy were to discontinue NSAIDs or to replace the NSAIDs with drugs with a low risk of bleeding. Among 37 patients with a history of low-dose aspirin or NSAIDs medication, only 3 that were treated with selective cyclooxygenase (COX)-2 inhibitors had normal stool. Most patients with active bleeding during endoscopy had angioectasia (8 of 9 patients). A fecal occult blood test was performed in patients with normal stools (16 of 28) and results was negative in 12 of these patients, among which 7 had no SB lesions. A significantly higher frequency (40 of 51) of ulcerative/erosive lesions was observed in patients with inactive bleeding but visible SB lesions than other causes, among whom 62.5% (25 of 40) had a history of low-dose aspirin or NSAIDs medication. As a result, NSAID-induced enteropathy accounted for 41.7% (25 of 60) of all SB bleeding cases. Four cases of previously undiagnosed Crohn's disease 1 case of tuberculosis were identified. Other uncommon etiologies associated with unknown GI bleeding included radiation ileitis (n=3) and SB polyps (n=3).

## Evaluation of rebleeding and treatment

Prior to capsule endoscopy, 58 (69.9%) patients had anemia with hemoglobin <10 g/dL. SB bleeding was predominant in >50% (17 of 28) of patients with normal stool. All patients with SB bleeding due to angioectasia showed bloody stools, while ulcerative lesions were prevalent in patients with normal stool. Rebleeding occurred in 7 patients during the 12-month follow-up period (Table 3). Two patients with Crohn's disease who presented with persistent iron deficiency anemia required specific treatments. One patient who was considered as Crohn's disease initially, presented multiple lymphadenopathy during follow-up period and finally diagnosed to have tuberculosis. Among 2 patients with radiation ileitis, 1 underwent surgical treatment due to recurrent bloody stool, whereas the other patient with persistent iron deficiency anemia refused an SB resection. A patient with a rebleeding episode from angioectasia received surgery. At last, one patient who received NSAIDs to treat fibromyalgia for >2 years, presented with an ulcerative lesion, had unresolved anemia and showed recurrent abdominal pain, which lasted for >6 months, despite adequate iron administration and stopping NSAIDs. An abdominal CT revealed multiple strictures of the SB, eventually underwent segmental resection of the SB, through which 5 sites of stenosis in the distal ileum were identified (Figure 2). No recurrence of anemia or abdominal pain was present 6-month postoperatively.

## Discussion

Capsule endoscopy for unexplained GI bleeding has shown diagnostic yields of 57–62%,<sup>24</sup> with the most common diagnosis being angioectasia (50%), followed by ulcers (26.8%) and tumors (8.8%), as suggested in a recent systematic literature review.<sup>14</sup> The present study revealed a detection rate of SB bleeding and lesions using capsule endoscopy of 72.3% (60 of 83 patients), of which NSAID-induced enteropathy accounted for 41.7% (25 of 60) of all SB bleeding cases. The diagnostic yield of small bowel lesions from our study was higher than a previous nationwide Korean study of capsule endoscopy,<sup>25</sup> but the prevalence of ulcerative/erosive lesions was comparable (66.7%, 40/60 vs 67.5%, 106/157). Similar to our results, a Korean study using balloon-assisted enteroscopy found the most common type of SB lesions associated with obscure GI bleeding was mucosal injury (56%), followed by vascular lesions (18.7%)<sup>26</sup> Because of limited availability of data regarding the use of NSAIDs/low-dose aspirin, we could not compare the prevalence of NSAID-induced enteropathy with results from these studies. However, considering the meaningful association between NSAID use and SB injury presented in previous studies,<sup>22, 27</sup> NSAID-induced enteropathy could be the major cause of obscure GI bleeding in Eastern countries. Contrary to previous reports from Western countries, we observed a higher occurrence rate of ulcerative/erosive lesions than angioectasia in patients with obscure GI bleeding, supporting the implication of low-dose aspirin or NSAID medications in the disease etiology.

NSAIDs are frequently used anti-inflammatory analgesic agents that represent 7.7% of worldwide prescriptions, of which 90% are prescribed to elderly (> 65 years) patients.<sup>28</sup> The mechanism of NSAID-induced enteropathy is supposed to be mediated through COX inhibition.<sup>29</sup> Administration of low-dose aspirin (irreversible nonselective COX inhibitor) is also associated with SB mucosal injuries; large erosions or ulcers were reported in 60% of healthy volunteers who took 100 mg of low-dose enteric-coated

aspirin.<sup>30,31</sup> In the present study, a history of low-dose aspirin or NSAID use was common in patients with obscure GI bleeding (44.6%), showing a higher frequency of SB ulcerative lesions (68%) than of other sources of lesions (angioectasia, n = 6; upper or lower GI bleeding, n = 6).

Prostaglandins (PG) play an important role in regulating GI blood flow and mucus production; therefore, NSAID-induced suppression of PG production has been implicated in SB damage.<sup>32,33</sup> Previously, COX-1 inhibition was regarded to be dominantly related to GI mucosal injuries. However, in a recent animal model study, damage to the SB developed only when both COX-1 and COX-2 were inhibited.<sup>34</sup> This result indicates that COX-2-derived PGs also play an important role in the maintenance of tissue integrity and repair of mucosal injury. However, clinical research has shown conflicting results. Several studies showed an improved GI safety profile with selective COX-2 inhibitors compared to nonselective NSAIDs,<sup>35,36</sup> while others studies indicated no significant differences in SB injuries between these NSAIDs.<sup>37,38</sup> In the current study, among 37 patients with a history of low-dose aspirin or NSAID medications, the 3 patients treated with the selective COX-2 inhibitors had normal stool, suggesting favorable GI outcomes with selective COX-2 inhibitor therapy. Considering that selective COX-2 inhibitors are not completely safe for the SB, further long-term studies with a larger sample size are warranted to establish the safety profile of the drug in the SB.

Furthermore, the impact of capsule endoscopy on clinical outcomes remains controversial despite reports of SB mucosal damage in 70% of patients taking NSAIDs,<sup>22,39</sup> because it remains unclear whether SB mucosal injuries contribute to significant bleeding.<sup>40</sup> Although patients with NSAID-induced SB injury show low frequency of severe bleeding in the SB,<sup>41</sup> rebleeding rates of 21–35% have been reported in patients with SB ulcerations during a mean follow-up period of 17.1–29.7 months.<sup>15,42</sup> These reports suggest a clinical implication of SB ulcers, which cannot be ignored.

The most effective method of preventing NSAID-induced enteropathy is discontinuation of NSAIDs if it is possible.<sup>12</sup> Previously there was no strategy to prevent NSAID-induced enteropathy.<sup>13,43</sup> However, a recent study reported the effectiveness of misoprostol in the treatment of SB ulcer bleeding associated with aspirin.<sup>44</sup> On the contrary, lesions that induce stenosis, which may not be treated with medication alone, require endoscopic or surgical interventions.<sup>45</sup> In the present study, a patient suffering from fibromyalgia developed SB stricture after NSAID medications for > 2 years and eventually underwent surgical resection.

This study has several limitations. First, it was a retrospective analysis with a small sample size that with insufficient power to detect a significant effect. Second, because balloon-assisted enteroscopy was not routinely performed, pathological findings could not confirm SB ulcers. Third, the short follow-up period prevented the adequate assessment of risk factors for rebleeding. Finally, the fecal occult blood test could not be performed in approximately 50% (12 of 28) of patients who presented with normal stools, thereby limiting the interpretation of the results.

# Conclusions

This study showed an improved diagnostic yield of capsule endoscopy for obscure GI bleeding and reaffirmed that NSAID-induced enteropathy is the most common etiology of SB bleeding in Korean patients. Therefore, aggressive clinical management, including SB capsule endoscopy, should be considered for patients with unexplained GI bleeding or drug-refractory iron deficiency anemia, particularly during aspirin or NSAID medications.

# Abbreviations

GI, gastrointestinal; SB, small bowel; NSAIDs, nonsteroidal anti-inflammatory drugs; COX, cyclooxygenase; PG, prostaglandin; CT, computed tomography

# Declarations

## Acknowledgement

Not Applicable.

## Author contributions

Study coordination and drafting of the manuscript: DHL and KJ. Study coordination and critical review of the manuscript: DHL and LSB. Review of capsule endoscopy images: KJ, LSB, JHP, JHK, and SEK. Data supply and approval of the final version of this manuscript: IKP, HJC, BGK, IDJ, and MW. Data analysis and approval of the final version of this manuscript: SWJ, MIP, and SJP. All authors read and approved the final manuscript.

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## Availability of data and materials

The datasets used and/or analyzed during the current study available from the corresponding author on request.

## Ethics approval and consent to participate

This study was approved by the Institutional Review Board (IRB, the local ethical committee) of the Ulsan University Hospital (IRB No. 2019-10-014) and the Kosin University Gospel Hospital (IRB No. 2019-10-001).

## Consent for publication

Not applicable. The requirement for informed consent of patients was waived by IRB because patient records and information were de-identified.

## Competing interests

The authors declare no competing interests.

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## Tables

Table 1. Clinical characteristics of patients

Characteristics	Overall (n=83)	Bloody stool (n=55)	Normal stool (n=28)	p-value
Age, yr.	59 ± 18	61 ± 19	56 ± 15	0.185
Sex, male	52 (62.7)	37 (67.3)	15 (53.6)	0.222
Aspirin/NSAID	37 (44.6)	25 (45.5)	12 (42.9)	0.822
Hemoglobin (g/dL)	8.7 ± 3.0	8.7 ± 2.8	8.9 ± 3.5	0.785
Albumin (g/dL)	3.8 ± 0.6	3.7 ± 0.7	3.9 ± 0.6	0.191
Small bowel bleeding	60 (72.3)	43 (78.2)	17 (60.7)	0.093
Specific lesion*				
Angioectasia	14 (23.3)	14 (32.6)	0 (0.0)	
NSAID-induced enteropathy	25 (41.7)	15 (34.9)	10 (58.8)	0.024
Other causes†	21 (35.0)	14 (32.6)	7 (41.2)	
Site of bleeding*				
Jejunum	16 (26.7)	14 (36.2)	2 (11.8)	
Ileum	38 (63.3)	26 (60.5)	12 (70.6)	0.169
Indeterminate	6 (10.0)	3 (7.0)	3 (17.6)	

\*The denominator is 60 patients with confirmed small bowel lesion.

†Other causes of small bowel bleeding, including Crohn's disease, intestinal tuberculosis, radiation ileitis, small bowel polyps, and small bowel lesions with unknown causes.

Categorical and continuous variables are presented as number (%) and mean ± SD, respectively.

SD, standard deviation; NSAID, nonsteroidal anti-inflammatory drug; Hb, hemoglobin.

Table 2. Details of NSAID/low-dose aspirin

	N=37 (100%) (NSAID=17 / Low-dose aspirin=21)*
<b>Indication</b>	
Coronary artery disease	11 (29.7)
Other cardiovascular disease	9 (24.3)
Musculoskeletal disease	15 (40.5)
Unknown	3 (8.1)
<b>Duration</b>	
<1 month	2 (5.4)
1-6 months	11 (29.7)
>6 months	22 (59.5)
Unknown	2 (5.4)
<b>Concurrent medication</b>	
Clopidogrel	6 (16.2)
Warfarin/NOAC	7 (18.9)
Other anti-platelet agent	3 (8.1)
None	21 (56.8)
<b>Site of bleeding</b>	
Small bowel	33 (89.2)
Stomach	2 (5.4)
Undetermined	2 (5.4)
<b>Etiology of small bowel bleeding†</b>	
NSAID-induced enteropathy	25 (75.8)
Angioectasia	7 (21.2)
Others	1 (3.0)
<b>Initial management of NSAID-induced enteropathy‡</b>	
Discontinue NSAID/low-dose aspirin	20 (80.0)
Continue NSAID/low-dose aspirin + Mucosal protective agent§	2 (8.0)
Unknown	3 (12.0)

\* One patient had a history of both NSAID and low dose aspirin.

† The denominator is 33 patients with confirmed small bowel bleeding on capsule endoscopy.

‡ The denominator is 25 patients with small bowel bleeding associated with NSAID/low-dose aspirin.

§ Mucosal protective agent indicates rebamipide, sucralfate, or sodium alginate.

NSAID, nonsteroidal anti-inflammatory drug; NOAC, non-vitamin K antagonist oral anticoagulant.

Table 3. Rebleeding cases

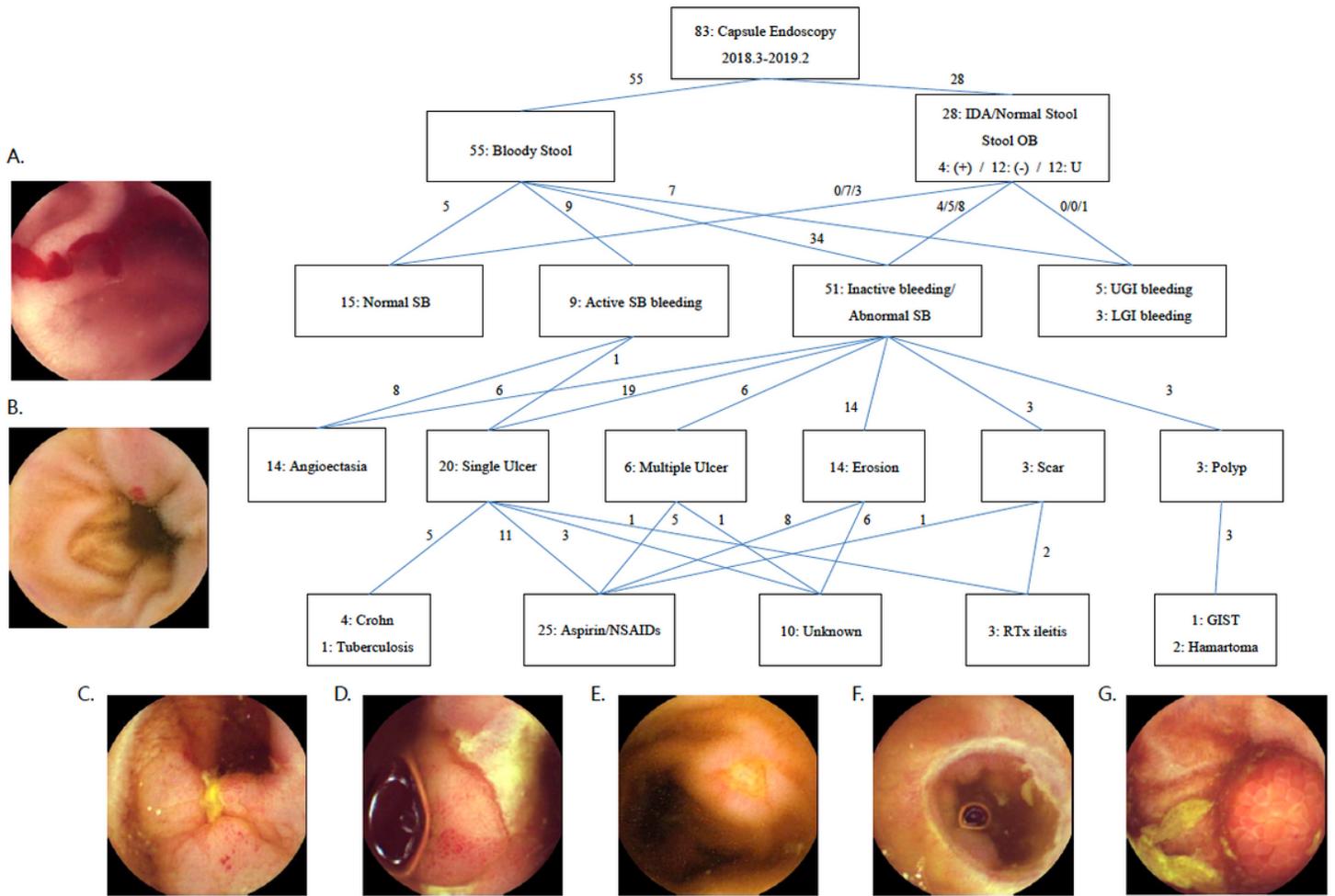
No.	Indication of capsule endoscopy	Cause of small bowel bleeding	Final diagnosis	Timing of rebleeding after diagnosis	Specific therapy	Treatment outcome
1	Bloody stool	Ulcer	Crohn's disease	23 days	Thiopurine	Persistent IDA
2	Bloody stool	Diffuse scar change	Radiation ileitis*	87 days	Surgery	No further bleeding
3	Bloody stool	Ulcer	Crohn's disease	117 days	5-aminosalicylic acid	Persistent IDA
4	Bloody stool	Ulcer with stricture	Radiation ileitis*	49 days	Refuse surgery	Follow up loss
5	IDA	Ulcer	Intestinal Tbc†	146 days	Anti-Tbc medication	Recovered IDA
6	IDA	Ulcer with stricture	NSAID-induced enteropathy	15 days	Surgery	Recovered IDA
7	Bloody stool	Angioectasia	Angioectasia	330 days	Surgery	No further bleeding

\* Indication of radiation therapy was uterine cervical cancer.

† The patient who was considered as Crohn's disease initially, presented multiple lymphadenopathy and finally diagnosed to have tuberculosis.

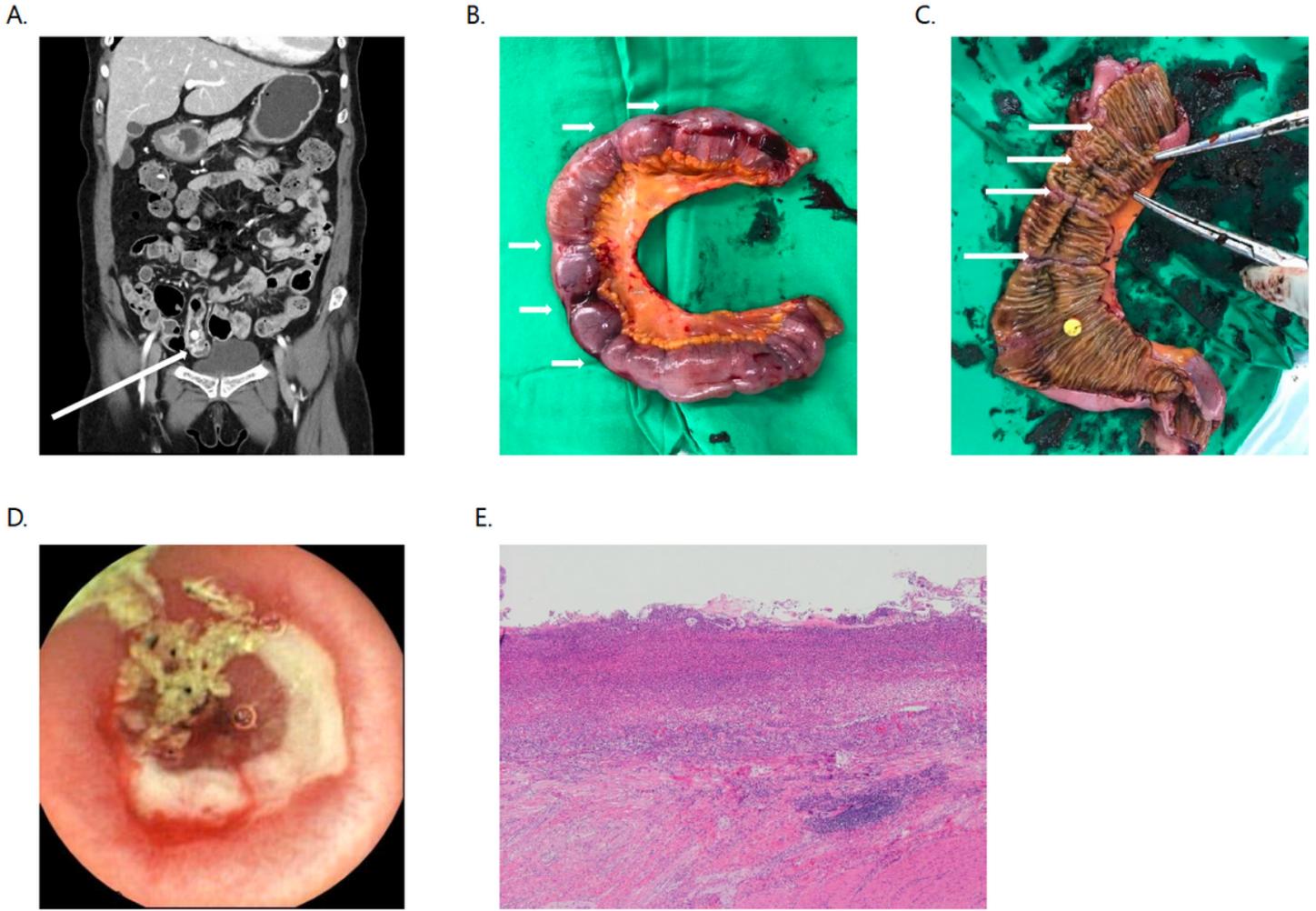
IDA, iron deficiency anemia; Tbc, tuberculosis; NSAID, nonsteroidal anti-inflammatory drug.

## Figures



**Figure 1**

Representative capsule endoscopy images of small bowel lesions. A. Angioectasia with active bleeding. B. Angioectasia with no bleeding. C. Crohn's disease. D. NSAID-induced enteropathy (ulcer). E. NSAID-induced enteropathy (erosion). F. Radiation ileitis. G. SB polyp (GIST). IDA, iron deficiency anemia; OB, occult blood; SB, small bowel; UGI, upper gastrointestinal; LGI, lower gastrointestinal; NSAIDs, nonsteroidal anti-inflammatory drugs; RTx, radiotherapy; GIST, gastrointestinal stromal tumor.



**Figure 2**

Surgical intervention in a patient with small-bowel stricture. A. Abdominal computed tomography showing stricture in the distal ileum. B. Gross findings after bowel resection with multiple stricture sites. C. Surgical resection exposing the inside of the small bowel. D. Capsule endoscopy image showing semi-circular ulcer with active hemorrhage. E. Histologic findings show ulceration including diffuse loss of villi, mucosal and submucosal neutrophilic exudates, and transmural inflammation (Hematoxylin and Eosin x40).