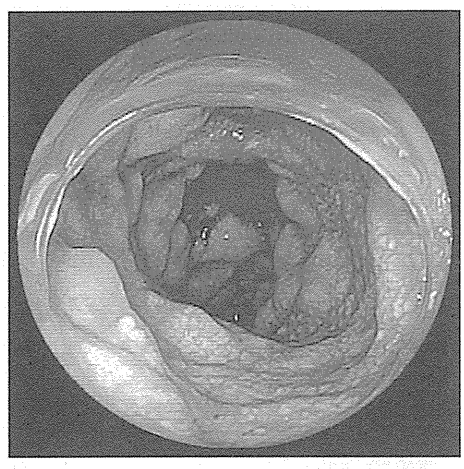


図 1. 小腸リンパ管腫
ダブルバルーン内視鏡像

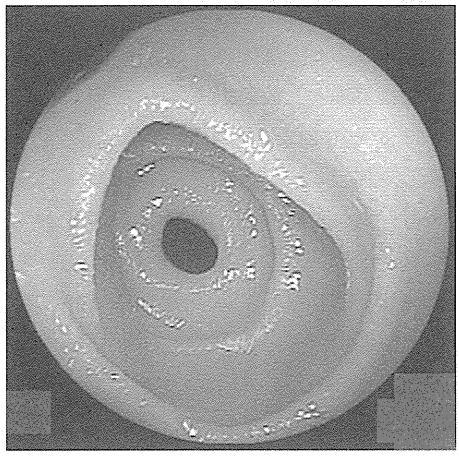


図 2. 膜様狭窄
ダブルバルーン内視鏡像

が増加した．結果として腫瘍性病変の検出割合が減少し潰瘍性病変の割合が増加する傾向にある．表 2 にOGIBの出血源となる主な病変を列挙したが，以下に病変について概略を示す．各項目の詳細については今号の特集を参考に願いたい．

1）中部消化管腫瘍性病変

ダブルバルーン内視鏡を用いて 1,035 例を分析した本邦の多施設共同研究でOGIBの出血源として 39 例の小腸腫瘍を診断・分析し，44％ がgas-

表 2. 原因不明消化管出血の主な出血源

Main source of obscure gastrointestinal bleeding
Mid Gastrointestinal Tract
Neoplastic lesion
Adenocarcinoma
Gastrointestinal stromal tumor : GIST
Lymphoma
Carcinoid
Polyp（inflammatory polyp, adenoma, etc）
Metastases（lung cancer, etc）
Hemangioma
Lymphangioma
Vascular lesion
Angioectasia（Angiodysplasia）
Dieulafoy lesion
Arteriovenous malformation（AVM）
Varicess
Radiation enteritis
Inflammatory lesion
Inflammatory bowel disease (Crohn's disease, etc)
NSAIDs-induced enteropathy
Infection (tuberculosis, cytomegalovirus, etc)
Other leson
Diverticulum (Meckel diverticulum, etc)
Henoch-Schönlein purpura
Extra Mid Gastrointestinal Tract
Esophagus
Varicess
Esophagitis
Stomach
Ulcer
Gastric antral vascular ectasia（GAVE）
Varicess
Duodenum
Ulcer
Diverticulum
Colon
Diverticulum
Angioectasia
Hemorrhoid

trointestinal stromal tumor（GIST），13% が転移性もしくは多臓器癌の直接浸潤，原発小腸癌8%，カルチノイド8% と報告された[5]．2010年のICCDで小腸悪性腫瘍の70% から90% は出血し，OGIBの病態になると報告された．現在広まっているOGIBの精査で小腸悪性腫瘍の術前診断率は増加すると推定される．さらに，FDG-PET（fluorodeoxyglucose-positron emission tomography）で小腸腫瘍の中でも癌，リンパ腫，GISTは高頻度に描出できるため，FDG-PETを用いた健診で小腸悪性腫瘍が多く発見されるものと考えられる[6]．どのくらいの割合，大きさの小腸腫瘍がPETで指摘できるのかは今後の検討課題であるが，今後小腸腫瘍の比較的早期発見が増加し，病態や治療法の進歩が期待される．

2）中部消化管血管性病変

国内外でOGIBの出血源の半数近くを占める主要な出血源が血管性病変である．血管性病変は図3のangioectasiaのように小型の病変が多く出血源として同定するのが困難な場合が少なくない．この血管性病変の中には，小さいにもかかわらず大量出血を引き起こす潜在力を有した病変がある．これら微少病変は止血すると発見が困難となる[1~4]．しかも，angioectasiaは複数同時に生じる場合があり，止血時には出血源かどうか確定できないばかりか，数カ所治療しても他のangioectasiaから出血する場合があり治療の容易でない病変である．特に肝硬変，慢性腎不全，Osler-Rendu-Weber症候群で病変は多発し，根治が困難である．血管性病変から出血している場合には，バルーン内視鏡検査が有用でangioectasiaのような小病変から出血していることが確認できればそのまま内視鏡治療を行うことができる．また，血管造影検査も非常に有用で出血部位を確認できれば，内視鏡治療が難しいarteriovenous malformation（AVM）でさえ治療が可能な場合がある．血管性病変では再出血を伴うことが少なくない．OGIBの再出血では，出血早期に検査を施行することが重要で，出血時になら100% 近い診断率であるが，出血2日後には50% 程に低下し以後診断率はさらに低下する．

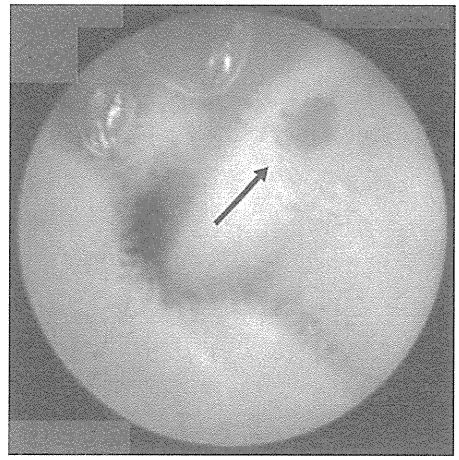


図3．angioectasia
カプセル内視鏡像

3）中部消化管潰瘍性病変

小腸潰瘍性病変には，結核などの感染症の他に，Crohn病・単純性潰瘍・Behçet病など原因が十分解明されていない疾患が多く含まれている．小腸に病変が限局する場合はOGIBの病態になりやすい．潰瘍性病変は本邦健常者においても10% 近くにびらん・潰瘍が認められるなどまだ未解明の多い分野である[7]．内科を専門とする今号の特集にあたり，NSAID起因性小腸傷害について少し詳細に述べたい．

OGIBの原因として10% を超える割合を呈しているものにNSAID起因性小腸粘膜傷害がある．NSAIDによる消化管副作用は患者を死に至らしめることがあり，米国では1998年にNSAIDによる消化管傷害で16,500人が死亡し，これは同年のAIDS（acquired immunodeficiency syndrome）による死亡者とほぼ同数であった[8]．1990年代にNSAIDを投与しているリウマチ患者が合併した重大な消化管傷害の約40% は下部消化管に起こったことが報告されたが，今世紀に入って急速に進歩したカプセル内視鏡やバルーン内

視鏡はアスピリンを含むNSAIDによって小腸にびらん，潰瘍，膜様狭窄などのさまざまな病変が高頻度に起こることを証明した[9]．ダブルバルーン内視鏡を用いた本邦多施設共同研究で，小腸粘膜障害（mucosal break）はNSAID非服用者では5％にしか指摘されなかったのに対して，NSAID服用者では51％の患者に指摘された[10]．また，通常型NSAIDを健常者に2週間投与する複数の試験で50％以上の服用者に小腸粘膜障害が生じ，NSAIDによる小腸粘膜傷害の発生頻度は高いことが明らかとなった[9]．

死亡例が胃・十二指腸潰瘍を発症したものに多く検査も容易であったことから，NSAID起因性消化管傷害の研究は近年まで上部消化管に重点がおかれてきた．これらの研究から，NSAID起因性の上部消化管潰瘍性病変を予防する方法としてプロトンポンプ阻害薬（PPI）やプロスタグランディン製剤（PG）を使用する方法が確立された[11]．NSAIDによる上部消化管傷害は防御法が確立したため，重大な上部消化管副作用は減少傾向にある．スペインではNSAIDによる下部消化管傷害に対する上部消化管傷害の頻度は1996年度は4.1倍であったが2005年には1.4倍となり，上部消化管傷害は減少し，下部消化管傷害とほぼ等しくなってきたと報告され，今後は下部消化管の防御法の確立が急務となっている[11]．NSAID小腸粘膜傷害はcyclooxygenase-1（COX-1）阻害や薬剤の直接作用による小腸粘膜の透過性の亢進に始まり，粘膜下に腸内細菌や消化液などの腸管内容が侵入することで，炎症が惹起するものと考えられている．薬剤濃度，消化液濃度，腸内細菌の分布は長い小腸内で異なることから，小腸潰瘍は小腸肛門側に多いなど病変の分布が部位で異なる傾向がある[12]．

治療法は残念ながら確立していない．通常型NSAIDの代わりにCOX-2選択的阻害薬の投与が理論上有効と考えられるが，COX-2選択的阻害薬の2週間投与は通常型NSAIDより小腸粘膜傷害が少ないとする報告がある一方，3カ月投与では発生頻度は変わらないとする報告があり，COX-2選択的阻害薬の評価はまだ不十分である[9]．われわれはPG製剤が有意に短期間のNSAID投与における小腸粘膜傷害を抑制することを報告し[7]，他施設でも低容量アスピリンの小腸粘膜傷害を改善することが報告されたため[13]，PG製剤は予防薬の候補として有望と考えている．そのほかにもレバミピド，メトロニダゾール，サルファサラジンの同時投与が有効である可能性が報告されている[9,14]．いずれにせよ十分な規模の臨床試験による有効性評価の確立が望まれる．

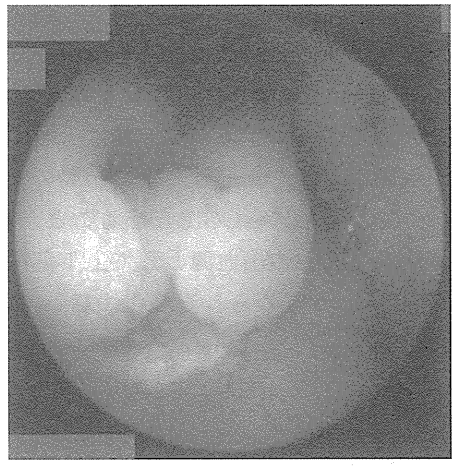


図4．dark-side of the pylorus
カプセル内視鏡像

4）そのほかの病変

中部消化管では他にも憩室が出血源となることがある．Meckel憩室は若年男性のOGIBの原因として中部消化管ではCrohn病の次に可能性が高い．高齢者では主に空腸に大型の憩室が多発することがある．また，前記したようにOGIBは中部消化管出血と同義ではない．胃や大腸に血管性病変を認めるが，止血しているために出血源が不明な場合が含まれている．また大腸憩室は出血が捉えられない場合，出血源として疑わしいが確信できないことが少なくない．さらに，当院でOGIBとして精査を受けた患者の約2％が

十二指腸潰瘍であった．潰瘍が通常内視鏡で観察困難な幽門輪の肛門側（dark-side of pylorus）に生じる症例があり，われわれもこの部位にNSAID潰瘍を認めた（図4）[15]．他にも十二指腸潰瘍治療後で，強く変形した十二指腸の死角に潰瘍が生じた場合にもOGIBとなることがある．このように，OGIBの出血源として上下部消化管病変が10％近く認められるため注意したい．

おわりに

カプセル内視鏡・バルーン内視鏡やそのほかの検査法の進歩は，今まで指摘できなかった多くの出血性病変を診断可能とした．頻回の出血や消化管出血による高度の貧血で悩む患者がいなくなるように，さらなる検査技術の進歩に加えて技術の習得が広まることを期待したい．

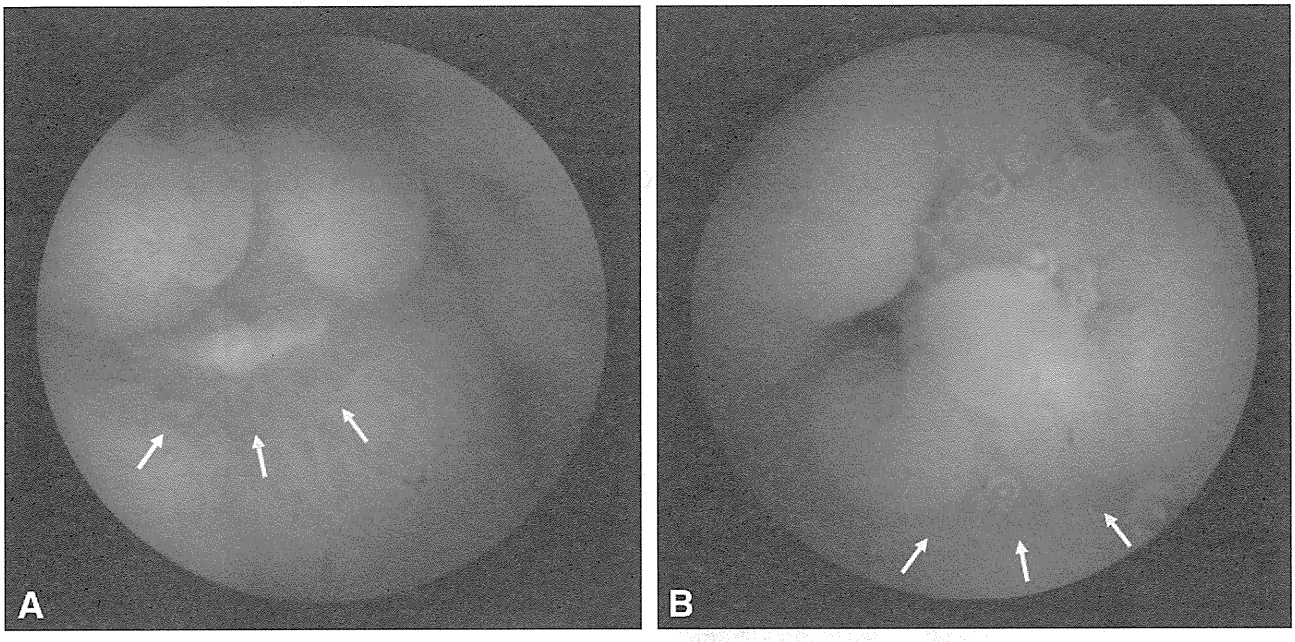
著者のCOI（conflicts of interest）開示：藤森俊二；旅費・贈答品（ギブン・イメージング），坂本長逸；講演料（アステラス製薬，エーザイ，大塚製薬，日本新薬），寄付金（アステラス製薬，エーザイ，シェリングプラウ），旅費・贈答品（ギブン・イメージング）

文　献

1) Pasha SF, et al : Diagnostic evaluation and management of obscure gastrointestinal bleeding : a changing paradigm. Gastroenterol Hepatol 5 : 839–850, 2009.
2) 藤森俊二，他：カプセル内視鏡とダブルバルーン内視鏡を併用した小腸内視鏡診断，治療の現況と将来．医学のあゆみ　220 : 243–247, 2007.
3) Fujimori S, et al : Diagnosis and treatment of obscure gastrointestinal bleeding using combined capsule endoscopy and double balloon endoscopy : 1-year follow-up study. Endoscopy 39 : 1053–1058, 2007.
4) Tanaka S, et al : Diagnostic yield of double-balloon endoscopy in patients with obscure GI bleeding. Gastrointest Endosc 68 : 683–691, 2008.
5) Mitsui K, et al : Role of double-balloon endoscopy in the diagnosis of small-bowel tumors : the first Japanese multicenter study. Gastrointest Endosc 70 : 498–504, 2009.
6) 藤森俊二，他：原発性小腸悪性腫瘍．日本臨床　66 : 1286–1296, 2008.
7) Fujimori S, et al : Prevention of nonsteroidal anti-inflammatory drug-induced small-intestinal injury by prostaglandin : a pilot randomized controlled trial evaluated by capsule endoscopy. Gastrointest Endosc 69 : 1339–1346, 2009.
8) Wolfe MM, et al : Gastrointestinal toxicity of nonsteroidal antiinflammatory drugs. N Engl J Med 340 : 1888–1899, 1999.
9) Fujimori S, et al : Prevention of traditional NSAID-induced small intestinal injury : recent preliminary studies using capsule endoscopy. Digestion 82 : 167–172, 2010.
10) Matsumoto T, 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.
11) Lanas A : Nonsteroidal antiinflammatory drugs and cyclooxygenase inhibition in the gastrointestinal tract : a trip from peptic ulcer to colon cancer. Am J Med Sci 338 : 96–106, 2009.
12) Fujimori S, et al : Distribution of small intestinal mucosal injuries as a result of NSAID administration. Eur J Clin Invest 40 : 504–510, 2010.
13) Watanabe T, et al : Small bowel injury by low-dose enteric-coated aspirin and treatment with misoprostol : a pilot study. Clin Gastroenterol Hepatol 6 : 1279–1282, 2008.
14) Higuchi K, et al : Present status and strategy of NSAIDs-induced small bowel injury. J Gastroenterol 44 : 879–888, 2009.
15) Takahashi Y, et al : The blind spot of an EGD : capsule endoscopy pinpointed the source of obscure gastrointestinal bleeding on the dark-side of the pylorus. Gastrointest Endosc in press.

Lawrence J. Brandt, MD, *Associate Editor for Focal Points*

The blind spot of an EGD: capsule endoscopy pinpointed the source of obscure GI bleeding on the dark side of the pylorus



The patient is a 58-year-old man with a 5-year history of hemodialysis for diabetic nephropathy, an 8-year history of aspirin use for angina pectoris, and a 4-year history of chronic anemia. He was referred to our institution for evaluation of obscure GI bleeding and melena. EGD and colonoscopy findings had been negative. Test results for *Helicobacter pylori* infection were negative. Laboratory test results revealed a progressing anemia with a recent hemoglobin decrease from 10.1 g/dL to 7.2 g/dL. Capsule endoscopy revealed an elliptical and well-demarcated ulcer with regenerating epithelium adjacent to the back side of the pylorus, also known as the "dark side" of the pylorus (**A**, *arrows*). Treatment with a proton pump inhibitor was given with resolution of melena and improvement in anemia. One year later, follow-up capsule endoscopy revealed the previously shown ulcer to have healed (**B**, *arrows*).

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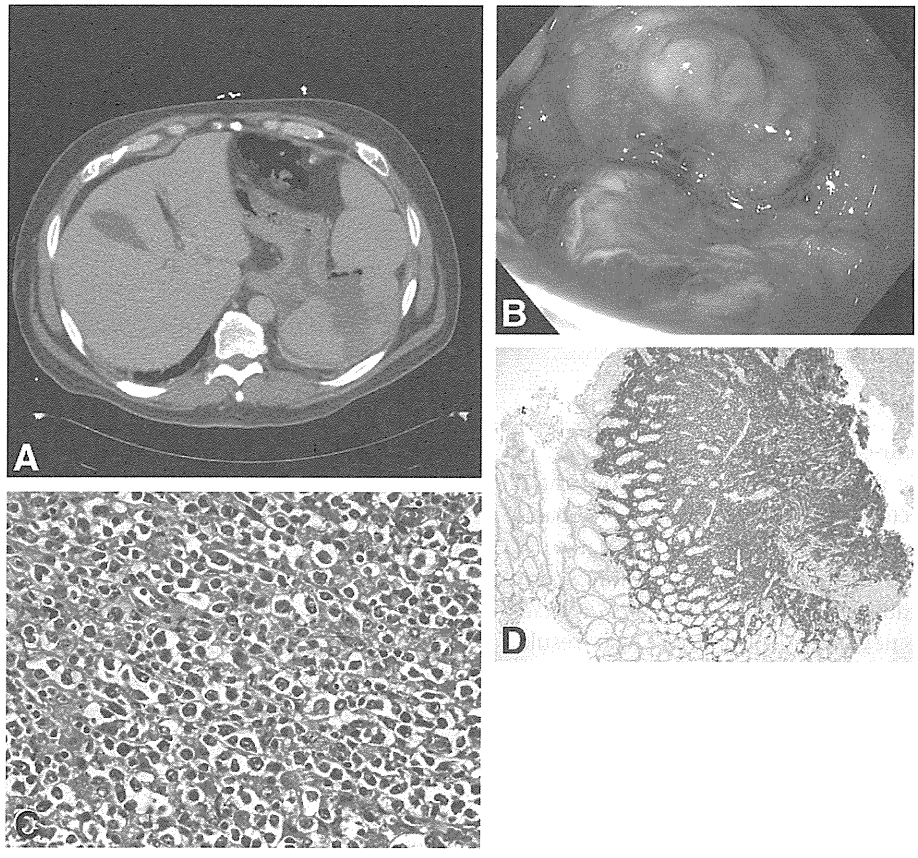
Commentary

The pylorus, a complex muscle structure, described by Torgersen in 1942 and thereafter also referred to as Torgersen's muscle, always has had a dark side. Mark Twain said that everyone is a moon and has a dark side that is never shown to anyone. And so it was until 2002, when I reported a case series in which I used an upper endoscope with an 8.9-mm outer channel to make a U turn in the duodenal bulb to view areas of gastric heterotopia and obtain biopsy specimens, some of which also had foci of

adenoma. I subsequently ablated the lesions with argon plasma coagulation, also performed with the endoscope in a retroverted position. Areas of the GI tract that have benefited from such retroinspection include not only the duodenum, but also the rectum and cecum. Indeed, the development of the Third Eye Retroscope (Avantis Medical Systems, Inc, Sunnyvale, Calif) attests to the need for such capability in the colon, and the videocapsule endoscope has extended our ability to look behind folds throughout almost the entire length of the GI tract. In the title of this Focal Point, the authors referred to the dark side of the duodenum as the blind spot of EGD. I wonder whether they knew that the physiological blind spot is also called the *punctum caecum*? A strange name when applied to an action in the duodenum. Henry David Thoreau, the American essayist, poet, and philosopher, said to never look back unless you are planning to go that way, but in gastroenterology, a look back at the dark side may provide the best means for a brighter future.

Lawrence J. Brandt, MD
Associate Editor for Focal Points

Spontaneous gastrosplenic fistula secondary to diffuse large B-cell lymphoma



A 55-year-old man with a remote history of diffuse large B-cell lymphoma presented to our institution with progressive weakness, fatigue, black stools for 1 week, and a hemoglobin of 9.0 g/dL (normal 14-18 g/dL). Examination revealed epigastric tenderness and a palpable spleen tip. A CT scan (**A**) showed a 1.4-cm, fistulous tract between the stomach and the splenic hilum, with a large splenic abscess. EGD with minimal air insufflation (**B**) revealed a large ulcer (2-3 cm wide, 7 cm deep) in the gastric fundus, with a deep tract, which was explored and lavaged. Cold forceps biopsy specimens of the ulcer and splenic tissue were obtained, which on immunohistochemistry showed

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ORIGINAL ARTICLE—ALIMENTARY TRACT

Rebamipide has the potential to reduce the intensity of NSAID-induced small intestinal injury: a double-blind, randomized, controlled trial evaluated by capsule endoscopy

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Abstract
Background A study reported that rebamipide was effective at reducing short-term nonsteroidal anti-inflammatory drug (NSAID)-induced enteropathy. The purpose of this study was to re-evaluate the effect of the co-administration of rebamipide on small intestinal injuries induced by short-term NSAID treatment.
Methods Eighty healthy male volunteers were randomly assigned to two study groups: a control group ($N = 40$), which received NSAID (diclofenac sodium, 75 mg/day) and omeprazole (20 mg/day) treatment along with a placebo; and a rebamipide group, which received NSAID, omeprazole and rebamipide (300 mg/day). Small intestinal injuries (mucosal breaks plus denuded areas) were evaluated by capsule endoscopy before and after 14 days of treatment.
Results A total of 38 control subjects and 34 rebamipide subjects completed the treatment and were evaluated by capsule endoscopy. NSAID therapy increased the mean number of mucosal injuries per subject from a basal level of 0.1 ± 0.3 to 16 ± 71 and 4.2 ± 7.8 in the control and rebamipide groups, respectively, but the difference was not significant. The difference in the percentage of subjects with at least one mucosal injury post-treatment was also not significant (control 63%; rebamipide 47%). Limiting our analysis to subjects with mucosal injuries, rebamipide co-treatment had the tendency to reduce the mean number of mucosal injuries per subject from 25 in the control group to 8.9 in the rebamipide group (multiple comparisons test; $p = 0.088$, Mann–Whitney U test; $p = 0.038$).
Conclusions Rebamipide co-therapy had the potential to reduce the intensity of small intestinal injury induced by 2-week administration of diclofenac.

Keywords Small intestinal injury · NSAID · Rebamipide · Prevention · Capsule endoscopy

Introduction

Nonsteroidal anti-inflammatory drugs (NSAIDs) are widely prescribed for patients with pain, inflammation and fever. However, it is well known that conventional NSAID use causes serious upper gastrointestinal complications, such as bleeding and perforation. These adverse events have been shown to occur in approximately 1–1.5% of patients within the first 12 months of treatment with NSAIDs [1–3]. It has also been shown that such NSAID-associated serious gastrointestinal complications occur not only in the upper but also in the lower gastrointestinal tract. A large-scale clinical trial revealed that the rate of serious lower gastrointestinal events is 0.9% per year in rheumatoid arthritis patients taking the nonselective NSAID naproxen [4]. NSAID medications have also been suggested as one of the major causes of obscure gastrointestinal bleeding, where the lesion responsible is often found in the small intestine.

Capsule endoscopy and double-balloon endoscopy, advanced modalities that now allow for full investigation of the entire small intestine, have revealed that NSAIDs cause a variety of abnormalities in the small intestine, including ulcerations, perforations, bleeding and diaphragm-like

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strictures [5–7]. Recent capsule endoscopy studies have shown that even short-term NSAID medication causes such small intestinal injuries in 50–70% of subjects [8–11]. These capsule endoscopy studies have also shown that even concomitant administration of proton pump inhibitors failed to prevent NSAID-induced small intestinal injury in healthy volunteers. Nevertheless, few studies have investigated how to prevent NSAID-associated lower gastrointestinal injuries, although celecoxib, a selective cyclooxygenase-2 (COX-2) inhibitor, caused minimal injuries [8, 10]. It was recently reported that the long-term use of COX-2 selective inhibitors was linked to an increased risk of cardiovascular events, and thus physicians have reverted to the prescription of conventional NSAIDs [12, 13]. Therefore, if this trend continues, the most logical approach is to consider protective measures against the gastrointestinal risk posed by conventional NSAIDs.

In our preliminary study, we have shown that co-administration of misoprostol reduced the incidence of small intestinal lesions induced by two-week administration of diclofenac [11]. However, misoprostol can induce intolerable side effects, as reported previously [14]. In addition to our study, another small preliminary study recently conducted by Niwa et al. has shown that rebamipide, a cytoprotective antiulcer agent widely prescribed in Asian countries [15–17], also effectively reduced the incidence of NSAID-associated small intestinal injury [18]. These results, which show the effectiveness of rebamipide against NSAID-induced small intestinal injury, are highly consistent with data from an animal experiment in which the intestinal injuries in rats were reduced with rebamipide, due to its free radical scavenging activity [19]. Furthermore, no clinical study to date has reported any side effects for rebamipide.

Therefore, the purpose of this study was to re-evaluate, as a large sample size study, the effect of rebamipide on the incidence and intensity of small intestinal injuries in healthy subjects on short-term NSAID treatment through a double-blind, randomized controlled capsule endoscopy trial.

Subjects and methods

Study subjects

A total of 80 healthy male subjects who had volunteered through open recruitment were screened by laboratory tests and interviews between July 2007 and March 2008. This study was approved by the Ethics Committee at Nippon Medical School, and all subjects provided written informed consent for enrolment in the study before undergoing baseline capsule endoscopies. This study was assigned to the ISRCTN Registry, a numeric system for the identification of randomized controlled trials conducted worldwide (ID: 50390099).

Inclusion/exclusion criteria

Eligible subjects were aged 20–50 years, had taken no medication during the 1-month period prior to the start of this study, and had normal physical examination and laboratory results. Exclusion criteria included failure to access the full length of the small intestine by capsule endoscopy, and the presence of stenosis, tumors, ulcers, or more than five mucosal breaks in the small intestine. Subjects were also excluded from this study if they had active gastrointestinal disease or a history of ulcers, a history of operation, bleeding, positive fecal occult blood test at screening, or hemoglobin levels <13 g/dl.

Capsule endoscopy

We used the Given video capsule system (PillCam®, Given Imaging Ltd., Yoqneam, Israel) for this study. The capsule endoscopy procedure and methodology for the review of images were conducted as previously described [20]. A skilled reviewer, who remained blinded to the subjects' treatment protocol, evaluated all video images for small intestinal injuries within a week following capsule endoscopy. All images were saved for final comprehensive analysis upon completion of all post-treatment capsule endoscopies.

Study protocol

Treatment protocol and post-treatment capsule endoscopy

Prior to baseline capsule endoscopy, all subjects were randomly divided into two groups, a control group ($n = 40$) and a rebamipide group ($n = 40$). After evaluation by baseline capsule endoscopy, all eligible subjects were administered diclofenac 25 mg three times daily and omeprazole 20 mg once daily immediately after meals for a period of 2 weeks. The control group was assigned to remain on the original diclofenac and omeprazole therapy with a lactose-filled placebo capsule administered three times daily, while the rebamipide group was assigned to receive a capsule filled with rebamipide 100 mg three times daily in addition to the original treatment (Fig. 1). An independent pharmacologist with no connection to our institution or the results of this study conducted the allocation and block randomization of patients. Post-treatment capsule endoscopy was performed within 24 h following completion of the drug regimen. Subjects that developed any symptoms warranting discontinuation of treatment or those with incomplete post-treatment capsule endoscopies were excluded from final analysis.

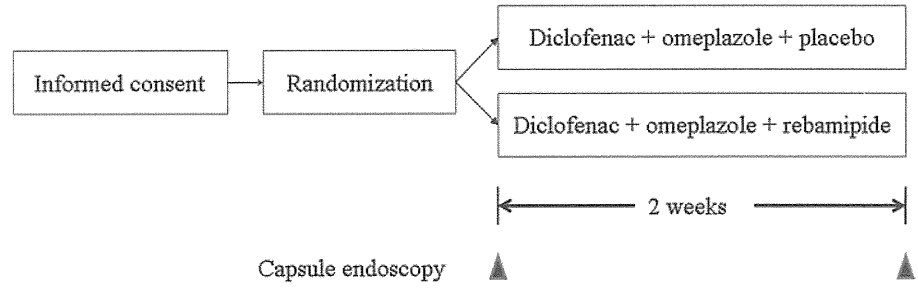

Fig. 1 Study design

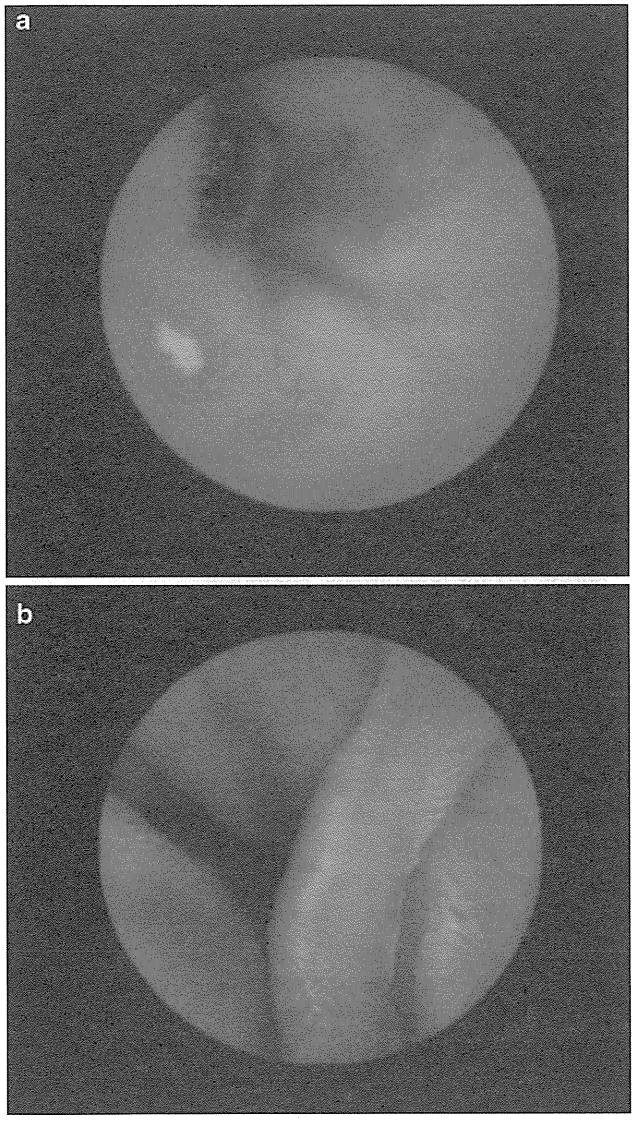

Fig. 2 **a** Example of a typical mucosal break found in this study. **b** Example of a typical denuded area found in this study

Evaluation of small intestinal injury

In this study, mucosal breaks of the small intestine were defined as lesions with slough surrounded by erythema. Neither the depth of ulcers nor the size of lesions were taken into consideration. Examples of typical mucosal breaks found in this study are shown in Fig. 2a. Denuded areas were defined as reddened areas without villi (Fig. 2b). Mucosal injuries consisted of both mucosal breaks and denuded areas in this study. The number of mucosal breaks and denuded areas of the small intestine found at baseline and post-treatment capsule endoscopy was calculated for each patient and compared between the rebamipide and control groups. Additionally, the percentage of subjects with at least one mucosal injury at post-treatment capsule endoscopy was compared between the rebamipide and control groups. In this study, the number of small intestinal injuries defined the degree of small intestinal injury. To evaluate the degree of NSAID-induced small intestinal injury, the number of small intestinal injuries per subject was evaluated for subjects in whom at least one mucosal injury was detected, and then compared between the two groups.

Sample size estimation

Sample size was based on our estimation of the proportion of patients that would exhibit mucosal breaks at post-treatment capsule endoscopy. We estimated that the incidence of mucosal injuries would be approximately 20% in the rebamipide group, based on data from a preliminary study by Niwa et al., showing that the incidence of NSAID-induced small intestinal lesions was lower in patients on daily rebamipide medication (20%) than in patients taking placebo (80%) [18]. In addition, we estimated that the incidence of mucosal injuries would be approximately 60% in the control group, because a recent study found small intestinal lesions in 7–14% of healthy subjects, compared with a rate of 55–68% in subjects on NSAID medication [8, 9, 11]. Thus, a two-sided test, with a significance level of 0.05 and a power of 90% ($\alpha = 0.05$, $\beta = 0.10$), would require 32 subjects per group. Assuming that 20% of the patients would not be able to complete the study, we calculated that a minimum of 40 subjects per group would be required for this study.

Statistical analyses

Characteristics of age, body weight, and body mass index were calculated by Student's t test. Characteristics of the

proportions of the subjects with mucosal breaks or denuded areas were calculated by Fisher's exact test. Characteristics of the numbers of mucosal breaks or denuded areas were calculated by the Mann–Whitney *U* test. The percentage of subjects with at least one mucosal injury, including mucosal breaks and denuded areas, at post-treatment capsule endoscopy was compared between the rebamipide and the control groups by Fisher's exact test. Interaction between medication and the before–after number of mucosal injuries in each group was evaluated by the Friedman test. In all subjects, and in subjects with at least one small intestinal injury, the mean number of small intestinal injuries per subject at baseline and post-treatment endoscopy were compared between the rebamipide and control groups by the Mann–Whitney *U* test and the post hoc multiple comparison test using the Hochberg test. Data were expressed as the mean value ± SD. *p* values <0.05 were considered significant.

Results

Analysis of subjects

The pool of prospective subjects consisted of 92 men with negative fecal occult blood tests and hemoglobin levels >13 g/dl at the time of screening. Twelve men were excluded from the study because three had a history of gastroduodenal ulcers, three a history of appendectomy, while six were under various medications. The remaining 80 subjects were randomized into either the placebo or the rebamipide group and underwent baseline capsule endoscopy. Among these subjects, 76 were found to have no significant pathology throughout the small intestine and were thus considered eligible for this study. Four subjects, one in the control group and three in the rebamipide group, were not eligible on the basis of our exclusion criteria because the entire small intestine could not be observed at their baseline capsule endoscopies. In addition, two subjects in the rebamipide group were later withdrawn from the study for medical reasons, one because of an influenza infection and the other due to systemic edema, a side effect of diclofenac. Two other subjects, one each in the placebo and rebamipide groups, were also excluded from our final analysis due to incomplete observation of the entire small intestine at post-treatment capsule endoscopy. Finally, small intestinal injuries were analyzed at post-treatment capsule endoscopy in 38 subjects in the control group and 34 subjects in the rebamipide group. The characteristics of each group's subjects, including age, body weight, body mass index, mucosal breaks, and denuded areas, are shown in Table 1.

Table 1 Characteristics of the analyzed subjects

Variables	Control	Rebamipide	*P* value
No.	38	34	
Age (years)	38 ± 8	37 ± 8	0.54[a]
Body weight (kg)	73 ± 9	70 ± 11	0.50[a]
Body mass index	24 ± 3	24 ± 3	0.74[a]
No. of subjects with mucosal breaks	1 (2.6%)	3 (8.8%)	0.34[b]
No. of mucosal breaks	0.1 ± 0.2	0.1 ± 0.3	0.65[c]
No. of subjects with denuded areas	3 (7.9%)	1 (2.9%)	0.62[b]
No. of denuded areas	0.1 ± 0.3	0.1 ± 0.2	0.71[c]

Mean ± SD

[a] *P* values were calculated by Student's *t* test

[b] *P* values were calculated by Fisher's exact test

[c] *P* values were calculated by the Mann–Whitney *U* test

Small intestinal injuries at baseline capsule endoscopy

One mucosal break and three denuded areas were found at baseline capsule endoscopy in the 38 subjects in the control group, and three mucosal breaks and one denuded area in the 34 subjects in the rebamipide group. There was no statistical difference at baseline capsule endoscopy between the two groups (Table 1). The percentage of subjects with at least one mucosal break and/or denuded area was 11% (8 out of 72) for both groups combined.

Mucosal injuries at post-treatment capsule endoscopy

Two-weeks of NSAID medication induced small intestinal injuries, including mucosal breaks and denuded areas, in both the control and rebamipide groups. In the control group, diclofenac treatment induced 515 mucosal breaks in 16 subjects and 88 denuded areas in 12 subjects, while NSAID medication together with rebamipide induced 86 mucosal breaks in 14 subjects and 57 denuded areas in 11 subjects. Thus, in the control group, both the percentage of subjects with at least one mucosal injury (mucosal breaks 42%; denuded areas 32%) and the mean number of mucosal injuries per subject (mucosal breaks 14 ± 71; denuded areas 2.3 ± 7.6) increased significantly in response to NSAID medication (all *p* values, $P < 0.01$). Despite rebamipide treatment, the differences in both the percentage of subjects with at least one mucosal injury and the mean number of mucosal injuries per subject before and after NSAID medication were also statistically significant in the rebamipide group ($P < 0.01$). There were no statistical interactions between medication and the before–after number of mucosal injuries in each group.

Although the incidence of mucosal injuries in response to NSAID medication was also significant in the

rebamipide group, the mean number of mucosal breaks per subject (2.5 ± 5.0) tended to be low as compared to that in the control group (14 ± 71). However, this difference between the two groups was not statistically significant. Similarly, the difference in the mean number of denuded areas per subject (2.3 ± 7.6 in the control group and 1.7 ± 4.0 in the rebamipide group) was also not statistically significant between the two groups. When mucosal breaks and denuded areas were combined in order to compare the total number of small intestinal injuries, the difference in the mean number of small intestinal injuries per subject (16 ± 71 in the control group and 4.2 ± 7.8 in the rebamipide group) was also not statistically significant. The difference in the percentage of subjects with at least one mucosal injury between the two groups was also not statistically significant (24 out of 38 subjects in the control group, i.e., 63%; 16 out of 34 subjects in the rebamipide group, i.e., 47%). Detailed data are shown in Table 2.

Comparison of the extent of injury between the two groups

Next, we compared the mean number of mucosal injuries per subject between the two groups only in subjects with injuries caused by NSAID medication in order to determine the extent to which rebamipide had affected subjects susceptible to NSAID-induced mucosal injury. For this analysis, mucosal breaks and denuded areas were also combined. In the rebamipide group, a total of 143 lesions were found in 16 subjects, resulting in a mean number of 8.9 ± 9.4 mucosal injuries per subject. This was lower than the mean number of 25 ± 89 lesions per subject (603 lesions in 24 subjects) in the control group (Hochberg test; $P = 0.088$, Mann–Whitney U test, $P = 0.038$), indicating that rebamipide had the potential to be effective at reducing the mean number of small intestinal injuries in those subjects susceptible to NSAID-induced mucosal injuries (Fig. 3).

Discussion

In the present study, rebamipide medication was not shown to be effective at reducing the incidence of diclofenac-induced small intestinal injury. However, the mean number of mucosal breaks and denuded areas per subject both tended to be lower in patients on rebamipide medication than in those in the control group. In addition, the percentage of subjects with at least one mucosal injury was also lower in the rebamipide group than in the control group. Furthermore, subanalysis restricted to subjects with small intestinal injuries showed that the mean number of mucosal injuries per subject tended to be lower in the rebamipide group than in the control group by post hoc multiple comparison test. These data suggest that rebamipide might be effective at reducing the intensity of NSAID-induced small intestinal injuries. However, one can argue that the effectiveness of rebamipide is questionable, because no statistical difference was detected between the two groups, and because a subject treated with diclofenac and rebamipide developed about 40 small intestinal mucosal injuries.

In the present study, we could not verify the effectiveness of rebamipide at reducing the incidence of NSAID-induced small intestinal injury, although, it did appear that rebamipide could in fact reduce the degree of small intestinal

Table 2 Comparison of the control group and the rebamipide group in terms of the number of subjects with small intestinal injuries at post-treatment capsule endoscopy

	Control	Rebamipide	*P* value
Number	38	34	
Mucosal breaks			
No. of subjects (%)	16 (42%)	14 (41%)	0.99[a]
Total no. of lesions (mean ± SD)	515 (14 ± 71)	86 (2.5 ± 5.0)	0.36[b]
Most no. of lesion per subject	427	18	
Median no. (25–75% value)	0 (0–1)	0 (0–1)	
Denuded areas			
No. of subjects (%)	12 (32%)	11 (32%)	0.99[a]
Total no. of lesions (mean ± SD)	88 (2.3 ± 7.6)	57 (1.7 ± 4.0)	0.66[b]
Most no. of lesion per subject	36	21	
Median no. (25–75% value)	0 (0–1)	0 (0–1)	
Total small intestinal injuries			
No. of subjects (%)	24 (63%)	16 (47%)	0.23[a]
Total no. of lesions (mean ± SD)	603 (16 ± 71)	143 (4.2 ± 7.8)	0.34[b]
Most no. of lesion per subject	427	39	
Median no. (25–75% value)	1 (0–4)	0 (0–5)	

[a] *P* values were calculated by Fisher's exact test

[b] *P* values were calculated by the Mann–Whitney *U* test

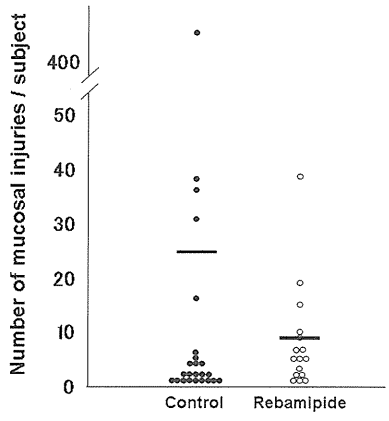

Fig. 3 Comparison of the mean number of mucosal injuries between the placebo and the rebamipide group in subjects with small intestinal injuries at post-treatment. *Note* that subjects with small intestinal injuries consisting of "mucosal breaks" and/or "denuded areas" at post-treatment were evaluated. *Closed circles* express the numbers of small intestinal mucosal injuries in the 24 subjects of the control group, and *open circles* express the numbers of small intestinal mucosal injuries in the 16 subjects of the rebamipide group. *P* values were 0.088 by Hochberg test and 0.038 by Mann–Whitney *U* test

damage in those subjects who developed injuries. Our results did not correspond with those of Niwa et al., who were able to show for the first time that rebamipide was effective at reducing the incidence of NSAID-induced small intestinal injuries [18]. Thus, we could not fully support the use of rebamipide as a therapeutic against NSAID-caused small intestinal injuries. In the present study, our sample size was estimated on the basis of the previous results [18]. Niwa et al. obtained their positive data in a crossover study where only ten subjects were treated with diclofenac in the presence or absence of rebamipide for 7 days. In such a preliminary study, where 7 days of NSAID-medication induced minor small intestinal injuries such as reddened patches and petechiae, the effect of rebamipide in preventing these types of injuries might have been overestimated. In our study, minor reddish lesions were not evaluated because it is difficult to get an accurate count of this type of lesion, and our 14-day diclofenac treatment induced sufficient mucosal breaks and denuded areas for us to be able to evaluate the prophylactic effect of repamipide. We have previously reported that there is no relation between mucosal breaks and denuded areas in the small intestine [21]. Therefore, we evaluated small intestinal mucosal breaks and denuded areas in this study. Even so, in that study, the incidence of NSAID-induced small intestinal lesions in patients on daily rebamipide medication was in fact lower than in the present study (20 vs. 47%). Thus, it seemed that had we used a larger sample size, we might then have found a significant reduction in the incidence of NSAID-induced small intestinal injuries in patients on rebamipide therapy. Furthermore, subanalysis restricted to subjects with small intestinal injuries at post-treatment should be planned before the study. Under this limitation, we found a statistical difference in the mean number of mucosal injuries per subject between the groups by the Mann–Whitney *U* test. Unfortunately, the subanalysis was not pre-planned, and a clear statistical difference was not obtained between the groups by the post hoc multiple comparison test. Therefore, in order to determine whether rebamipide is in fact a worthy candidate drug for the prevention of NSAID-induced small intestinal injury, a large-size study and a pre-planned subanalysis limited to subjects with small intestinal injuries at post-treatment are clearly required.

Nevertheless, this study has been able to show that rebamipide might be effective at preventing NSAID-induced small intestinal injuries to a certain extent. Rebamipide has been used across Asia for the treatment of gastric ulcers and gastric lesions such as erosions and edema caused by acute gastritis [14, 17, 22]. It has been well documented that rebamipide increases endogenous prostaglandin levels, scavenges free radicals, and suppresses inflammation in the gastric mucosa [23–25]. Through these actions, rebamipide has also been shown to be useful in preventing NSAID-induced gastrointestinal injuries in clinical studies and animal experiments. In a randomized controlled trial of rheumatoid arthritis and osteoarthritis patients carried out in East Asian countries, the effectiveness of rebamipide was shown to equal that of misoprostol in preventing the incidence of gastroduodenal ulcers caused by 12 weeks of NSAID medication [25]. As for NSAID-induced small intestinal injuries, a sequence of events such as an increase in the permeability of epithelial cells due to the direct toxic effect of NSAIDs, bacterial translocation, and inflammation through cytokine activation in the small intestinal mucosa have all been suggested to be key elements in the induction of small intestinal ulceration, in addition to a lack of prostaglandin [23, 26, 27]. In an animal experiment, rebamipide has been shown to inhibit increases in iNOS activity induced by indomethacin, thereby reducing small intestinal damage caused by NSAIDs in rats [19]. From all of these data, it is reasonable to speculate that, to some extent, rebamipide might serve to reduce small intestinal damage in patients on NSAID medication.

In the present study, several subjects incurred relatively high levels of small intestinal injury during NSAID treatment. Meanwhile, about 40% of subjects developed neither small intestinal mucosal breaks nor denuded areas after diclofenac and proton pump inhibitor treatment. The risk factor for upper gastrointestinal complications has been reported for patients on NSAID medication [28]. However, there is no evidence regarding the risk of small intestinal injury in this class of patients. Graham et al. [7] have shown

that the frequency of small intestinal injuries in patients who took nonselective NSAIDs over a three-month period was 71%. Goldstein et al. [8] and Maiden et al. [9] reported frequencies of 55 and 68% respectively for naproxen- and diclofenac-induced small intestinal injury in healthy subjects. Taken together, our results and those of others show that nonselective NSAIDs can cause small intestinal injuries in approximately 50–70% of subjects who were not known to be in danger of developing these types of injuries. However, before we can seriously consider rebamipide as a primary prophylactic against NSAID-induced small intestinal injury, we need to isolate those patient characteristics that are associated with this sort of injury, in order to determine which class of patients would derive any benefit from this type of therapy. Further study is required to determine the particular characteristics of subjects that render them susceptible to intense small intestinal damage.

In a preliminary study, we were able to verify the effectiveness of misoprostol at reducing the incidence of small intestinal lesions induced by two-week administration of diclofenac [11]. In addition, it is well known that misoprostol can prevent not only endoscopic gastroduodenal ulcers but also serious upper gastrointestinal complications such as perforation, obstruction and bleeding caused by NSAID medication in patients with rheumatoid arthritis or osteoarthritis. Considering the basis of the gastrointestinal side effects of NSAIDs, one would expect that misoprostol, a prostaglandin E1 analog, should be a promising drug for the prevention of the gastrointestinal side effects of NSAID medication. Nevertheless, proton pump inhibitors, which have been shown to be ineffective for the prevention of small intestinal damage, tend to be chosen over misoprostol for the prevention of NSAID-induced gastroduodenal injuries, mainly due to concerns regarding the unwelcome side effects of misoprostol, such as diarrhea and abdominal pain [14]. Therefore, the advent of a new drug against NSAID-induced upper and lower gastrointestinal damage that has no uncomfortable side effects is strongly desired.

In conclusion, we were not able to verify that rebamipide was in fact effective at reducing the incidence of NSAID-induced small intestinal injuries. Nevertheless, we found that rebamipide has the potential to reduce the intensity of injury in subjects who are apparently susceptible to NSAID-induced small intestinal injuries. Further extensive studies are clearly necessary to determine whether rebamipide is indeed a promising drug in the prevention of NSAID-induced small intestinal injury.

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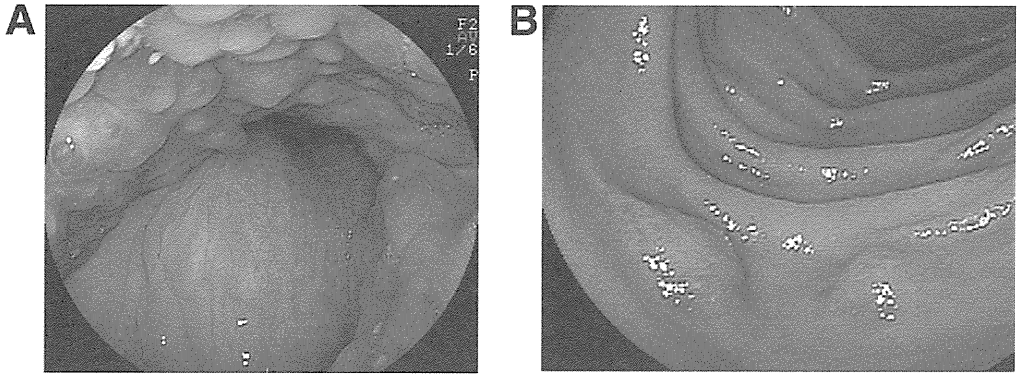
References

1. Silverstein FE, Graham DY, Senior JR, Davies HW, Struthers BJ, Bittman RM, et al. Misoprostol reduces serious gastrointestinal complications in patients with rheumatoid arthritis receiving nonsteroidal anti-inflammatory drugs. Ann Intern Med. 1995;123:241–9.
2. Silverstein FE, Faich G, Goldstein JL, Simon LS, Pincus T, Whelton A, et al. Gastrointestinal toxicity with celecoxib vs nonsteroidal anti-inflammatory drugs for osteoarthritis and rheumatoid arthritis: the CLASS study: a randomized controlled trial. Celecoxib Long-term Arthritis Safety Study. JAMA. 2000;284:1247–55.
3. Schnitzer TJ, Burmester GR, Mysler E, Hochberg MC, Doherty M, Ehrsam E, et al. Comparison of lumiracoxib with naproxen and ibuprofen in the Therapeutic Arthritis Research and Gastrointestinal Event Trial (TARGET), reduction in ulcer complications: randomized controlled trial. Lancet. 2004;364:665–74.
4. Bombadier C, Laine L, Reicin A, Shapiro D, Burgos-Vargas R, Davis B, et al. Comparison of upper gastrointestinal toxicity of rofecoxib and naproxen in patients with rheumatoid arthritis. VIGOR Study Group. N Engl J Med. 2000;343:1520–8.
5. Matsumoto T, Kudo T, Esaki M, Yano T, Yamamoto H, Sakamoto C, et al. Prevalence of non-steroidal anti-inflammatory drug-induced enteropathy determined by double-balloon endoscopy: a Japanese multicenter study. Scand J Gastroenterol. 2008;43:490–6.
6. Fujimori S, Seo T, Gudis K, Tanaka S, Mitsui K, Kobayashi T, et al. Diagnosis and treatment of obscure gastrointestinal bleeding using combined capsule endoscopy and double balloon endoscopy: 1-year follow-up study. Endoscopy. 2007;39:1053–8.
7. Graham DY, Opekun AR, Willingham FF, Qureshi WA. Visible small-intestinal mucosal injury in chronic NSAID users. Clin Gastroenterol Hepatol. 2005;3:55–9.
8. Goldstein JL, Eisen GM, Lewis B, Gralnek IM, Zlotnick S, Fort JG, et al. Video capsule endoscopy to prospectively assess small bowel injury with celecoxib, naproxen plus omeprazole, and placebo. Clin Gastroenterol Hepatol. 2005;3:133–41.
9. Maiden L, Thjodleifsson B, Theodors A, Gonzalez J, Bjarnason I. A quantitative analysis of NSAID-induced small bowel pathology by capsule endoscopy. Gastroenterology. 2005;128:1172–8.
10. Goldstein JL, Eisen GM, Lewis B, Gralnek IM, Aisenberg J, Bhadra P, et al. Small bowel mucosal injury is reduced in healthy subjects treated with celecoxib compared with ibuprofen plus omeprazole, as assessed by video capsule endoscopy. Aliment Pharmacol Ther. 2007;15:1211–22.
11. Fujimori S, Seo T, Gudis K, Ehara A, Kobayashi T, Mitsui K, et al. Prevention of NSAID-induced small intestinal injury by prostaglandin: a pilot randomized controlled trial evaluated by capsule endoscopy. Gastrointestinal Endosc. 2009;69:1339–46.
12. Mukherjee D, Nissen S, Topol EJ. Risk of cardiovascular events associated with selective COX-2 inhibitors. JAMA. 2001;286:954–9.
13. Baron JA, Sandler RS, Bresalier RS, Quan H, Riddell R, Lanas A, et al. A randomized trial of rofecoxib for the chemoprevention of colorectal adenomas. Gastroenterology. 2006;131:1674–82.
14. Park SH, Cho CS, Lee OY, Jun JB, Lin SR, Zhou LY, et al. Comparison of prevention of NSAID-induced gastrointestinal complications by rebamipide and misoprostol: a randomized, multicenter, controlled trial—STORM study. J Clin Biochem Nutr. 2007;40:148–55.
15. Yamasaki K, Ishiyama H, Imaizumi T, Kanbe T, Yabuuchi Y. Effect of OPC-12759, a novel antiulcer agent, on chronic and acute experimental gastric ulcer, and gastric secretion in rats. Jpn J Pharmacol. 1989;49:441–8.

16. Arakawa T, Watanabe T, Fukuda T, Yamasaki K, Kobayashi K. Rebamipide, a novel prostaglandin-inducer, accelerates healing and reduces relapse of acetic acid-induced rat gastric ulcer: comparison with cimetidine. Dig Dis Sci. 1995;40:2469–72.
17. Terano A, Arakawa T, Sugiyama T, Suzuki H, Joh T, Yoshikawa T, et al. Rebamipide, a gastro-protective and anti-inflammatory drug, promotes gastric ulcer healing following eradication therapy for *Helicobacter pylori* in a Japanese population: a randomized, double-blind, placebo-controlled trial. J Gastroenterol. 2007;42: 690–3.
18. Niwa Y, Nakamura M, Ohmiya N, Maeda O, Ando T, Itoh A, et al. Efficacy of rebamipide for diclofenac-induced small-intestinal mucosal injuries in healthy subjects: a prospective, randomized, double-blinded, placebo-controlled, cross-over study. J Gastroenterol. 2008;43:270–6.
19. Mizoguchi H, Ogawa Y, Kanatsu K, Tanaka A, Kato S, Takeuchi K. Protective effect of rebamipide on indomethacin-induced intestinal damage in rats. J Gastroenterol Hepatol. 2001;16: 1112–9.
20. Delvaux M, Gay G. Capsule endoscopy: technique and indications. Best Pract Res Clin Gastroenterol. 2008;22:813–37.
21. Fujimori S, Gudis K, Takahashi Y, Seo T, Yamada Y, Ehara A, et al. Distribution of small intestinal mucosal injuries as a result of NSAID administration. Eur J Clin Invest. 2010;40:504–10.
22. Kim HK, Kim JI, Kim JK, Han JY, Park SH, Choi KY, et al. Preventive effects of rebamipide on NSAID-induced gastric mucosal injury and reduction of gastric mucosal blood flow in healthy volunteers. Dig Dis Sci. 2007;52:1776–82.
23. Kent TH, Cardelli RM, Stamler FW. Small intestinal ulcers and intestinal flora in rats given indomethacin. Am J Pathol. 1969; 54:237–49.
24. Sakurai K, Sasabe H, Koga T, Konishi T. Mechanism of hydroxyl radical scavenging by rebamipide: identification of monohydroxylated rebamipide as a major reaction product. Free Radic Res. 2004;38:487–94.
25. Chitapanarux T, Praisontarangkul OA, Lertprasertsuke N. An open-labeled study of rebamipide treatment in chronic gastritis patients with dyspeptic symptoms refractory to proton pump inhibitors. Dig Dis Sci. 2008;53:2896–903.
26. Bjarnason I, Thjodleifsson B. Gastrointestinal toxicity of non-steroidal anti-inflammatory drugs: the effect of nimesulide compared with naproxen on the human gastrointestinal tract. Rheumatology. 1999;38(Suppl 1):24–32.
27. Bjarnason I, Hayllar J, MacPherson AJ, Russell AS. Side effects of nonsteroidal anti-inflammatory drugs on the small and large intestine in humans. Gastroenterology. 1993;104:1832–47.
28. Chan FK, Abraham NS, Scheiman JM, Laine L. Management of patients on nonsteroidal anti-inflammatory drugs: a clinical practice recommendation from the First International Working Party on Gastrointestinal and Cardiovascular Effects of Nonsteroidal Anti-inflammatory Drugs and Anti-platelet Agents. Am J Gastroenterol. 2008;103:2908–18.

Venous Varicosities in the Jejunum



Question: A 58-year-old man was admitted to our hospital, with relapsing anemia (hemoglobin [Hb], 6.9–8.8 g/dL) that responded to oral administration of iron for 3 years. He had undergone esophagogastroduodenoscopy and total colonoscopy, which demonstrated no bleeding sources 1 year earlier, and then underwent videocapsule endoscopy (VCE) 1 month earlier in another hospital. Because VCE showed multiple, solitary, venous dilations in the jejunum, he was referred to our hospital for further examination and management. His medical histories included vasospastic angina at 48 years of age, which had been treated on low-dose aspirin until hospitalization with anemia 1 year earlier with discontinuation thereafter, gout, urticaria, and ureterolithiasis. On examination, there were no abnormalities but scrotal angiokeratoma and sublingual venous dilation. Laboratory tests detected mild anemia (Hb, 10.3 g/dL) and liver dysfunction (aspartate aminotransferase, 58 IU/L; alanine aminotransferase, 49 IU/L) without hypoproteinemia (total protein, 7.5 g/dL; albumin, 4.0 g/dL) or thrombocytopenia (platelet count, 185 × 10^3/mm^3). Contrast-enhanced computed tomography and ultrasonography demonstrated fatty liver without cirrhosis, splenomegaly, or abnormal vessel structures such as varices. On the second hospital day, he underwent double-balloon enteroscopy (DBE) via the oral approach, which demonstrated multiple venous dilations with a caviar-like appearance at the base and pharyngeal portion of the tongue (Figure *A*), in the esophagus, and from the proximal to the mid jejunum (Figure *B*). What is the diagnosis and appropriate management for these jejunal lesions?

Look on page 738 for the answer and see the GASTROENTEROLOGY web site (www.gastrojournal.org) for more information on submitting your favorite image to Clinical Challenges and Images in GI.

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Conflicts of interest
The authors disclose no conflicts.

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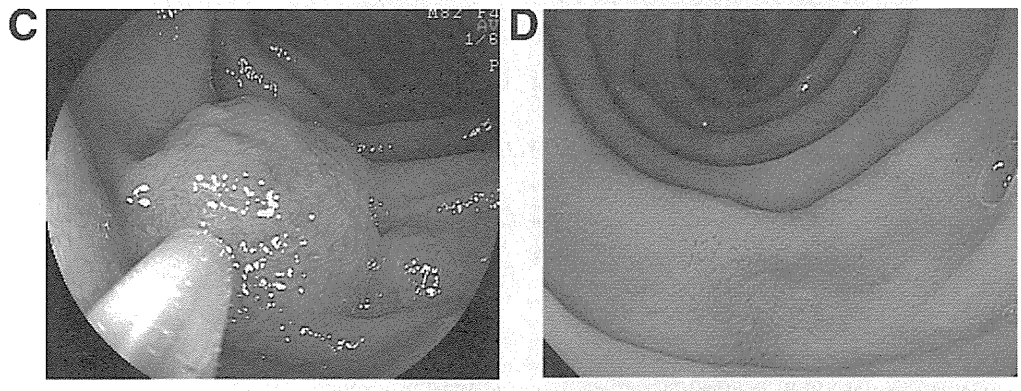

Answer to the Clinical Challenges and Images in GI Question: Image 2 (page 406): Intestinal Phlebectasias

At DBE, submucosal injection of 1.0% polidocanol solution into the periphery of the intestinal phlebectasias was performed (0.3–0.5 mL each; Figure *C*). In total, 22 mL of this solution was used as endoscopic injection sclerotherapy (EIS) for 29 phlebectasias. No gross bleeding or other adverse effects were encountered during or after treatment. Two months later, DBE was performed for follow-up. Almost all the jejunal phlebectasias had vanished completely, but a slight scar was observed in 1 lesion (Figure *D*). Laboratory testing detected no anemia (Hb, 14.5 g/dL).

Intestinal phlebectasias are venous varicosities, without portal hypertension, consisting of a markedly dilated tortuous vein with a normal vascular wall and scant connective tissue stroma. They occur primarily in elderly men. Phlebectasias may also occur in the oral cavity, mostly at the base of the tongue, where they are called caviar spots or sublingual phlebectasias, and in the scrotum. These cutaneous and oral findings are clues to the presence of intestinal lesions in elderly men with gastrointestinal bleeding.[1] The jejunum is the most commonly involved site, and so the lesions had usually been beyond the reach of a conventional endoscope before the advent of VCE and DBE.[2] As shown in this report, VCE is useful for screening and DBE enables endoscopic treatment for bleeding lesions deep within the small bowel.[3] Surgery has been the only definitive therapy for intestinal phlebectasias, but is employed sparingly because of their multiplicity and extent. The present report is the first to describe that EIS using polidocanol proved beneficial for extinguishing phlebectasias. With EIS, it is also easy to treat numerous lesions one after another repeatedly. Taken together, EIS with polidocanol for intestinal phlebectasias seems to be promising and may be preferable to surgery.

References

1. Cappell MS. Gastrointestinal vascular malformations or neoplasms: arterial, venous, arteriovenous, and capillary. In: Yamada T, ed. Textbook of gastroenterology. Oxford, UK: Wiley-Blackwell, 2009:2803.
2. Kumar P, Salcedo J, al-Kawas FH. Enteroscopic diagnosis of bleeding jejunal phlebectasia: a case report and review of literature. Gastrointest Endosc 1997;46:185–187.
3. Ohmiya N, Yano T, Yamamoto H, et al. Diagnosis and treatment of obscure GI bleeding at double balloon endoscopy. Gastrointest Endosc 2007;66(3 Suppl):S72–S77.

Endoscopic and Imaging Findings in Protein-losing Enteropathy

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Objectives: Protein-losing enteropathy (PLE) is often difficult to diagnose. We evaluated the diagnostic yields of underlying diseases of PLE among esophagogastroduodenoscopy, colonoscopy, fluoroscopic conventional enteroclysis (FCE), videocapsule endoscopy (VCE), and double-balloon enteroscopy (DBE) and prognosis after treatment.

Methods: Between June 2003 and August 2010, 25 consecutive patients with PLE confirmed by fecal α1-antitrypsin clearance (n = 18) and technetium 99m human serum albumin scintigraphy (n = 19) were enrolled, investigated, and treated.

Results: Of 25 patients, 4 (16%) with intestinal lymphangiectasia secondary to macroglobulinemia (n = 1), amyloidosis (n = 2), and strongyloidiasis (n = 1) were diagnosed at preceding esophagogastroduodenoscopy or colonoscopy, and 7 (32%) with primary intestinal lymphangiectasia and chronic nonspecific multiple ulcers unrelated to nonsteroidal anti-inflammatory drugs of the small intestine were newly diagnosed at FCE or VCE. Other 11 (44%) patients with primary intestinal lymphangiectasia, small-bowel tumors, amyloidosis, chronic nonspecific multiple ulcers unrelated to nonsteroidal anti-inflammatory drugs of the small intestine, Crohn's disease, and small-bowel ulcers due to polyarteritis nodosa were diagnosed only at DBE with biopsy. Three patients with primary intestinal lymphangiectasia, cirrhosis after living donor liver transplantation, and congestive heart failure were not diagnosed at any small-bowel examination. The overall diagnostic yield of FCE, VCE, and DBE was 62% (8/13), 83% (14/17), and 88% (22/25), respectively. Eight patients (32%) died of underlying disorders regardless of medical treatment over the follow-up period.

Conclusions: DBE with pathologic findings of biopsy specimens was useful for the differential diagnosis of PLE. Noninvasive VCE might be preferable and useful for screening and follow up of PLE without stricture. Prognosis of a subgroup of PLE was poor regardless of treatment.

Key Words: protein-losing enteropathy, fluoroscopic conventional enteroclysis, videocapsule endoscopy, double-balloon enteroscopy, prognosis

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Protein-losing enteropathy (PLE) is a rare and occasionally life-threatening syndrome characterized by enteric loss of plasma proteins in abnormal amounts, resulting in hypoproteinemia, which can be complicated by edema, ascites, pleural and pericardial effusions, and malnutrition. Although PLE is rare, it has many causes. The primary causes can be divided into ulcerative or nonulcerative enteropathies or occur secondary to lymphatic obstruction or increased lymphatic hydrostatic pressure.[1] Ulcerative diseases such as neoplasia (carcinoma and lymphoma), Crohn's disease, erosive enteritis, pseudomembranous enterocolitis, secondary amyloidosis, and acute graft-versus-host disease; nonulcerative diseases such as viral enteritides, bacterial overgrowth, parasitic diseases, Whipple disease, allergic enteritis, eosinophilic gastroenteritis, gluten-sensitive enteropathy, tropical sprue, polyposis syndromes, and systemic lupus erythematosus; and increased interstitial pressure such as in intestinal lymphangiectasia, mesenteric lymphatic obstruction, tuberculosis, sarcoidosis, lymphoma, retroperitoneal fibrosis, constrictive pericarditis, congestive heart failure, and Fontan procedure have been associated with PLE.[2] Especially, intestinal lymphangiectasia is the primary etiology of PLE due to lymphatic obstruction. As treatment of PLE targets the underlying disorders in addition to dietary modification and supportive care, the differential diagnosis is essential. The causes of PLE, however, sometimes remained undiagnosed with conventional imaging modalities such as esophagogastroduodenoscopy (EGD), colonoscopy, computed tomography (CT), and fluoroscopic conventional enteroclysis (FCE). Several recent case reports suggest that the latest enteroscopy modalities, double-balloon endoscopy (DBE) and videocapsule endoscopy (VCE), are useful for differential diagnosis of PLE.[3–8] However, there are few reports regarding the role of DBE and VCE in the diagnosis of PLE in a cohort study, compared with other examinations, and its prognosis. In the present study, we determined the roles of DBE and VCE in the diagnosis of underlying disorders in 25 patients with PLE, which was confirmed by fecal α1-antitrypsin (α1-AT) clearance and/or technetium (Tc) 99m human serum albumin scintigraphy, and the outcome after diagnosis.

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Y.H., M.N., E.O., R.M., H.K., A.I., O.W., and T.A. contributed to performing fluoroscopic enteroclysis, double-balloon enteroscopy, and videocapsule endoscopy.
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METHODS

Patients

Of 730 patients who were admitted to Nagoya University Hospital to undergo DBE between June 2003 and August 2010, 25 consecutive patients with PLE accompanied by hypoproteinemia were enrolled. Chief complaints of these patients were edema (n = 19), diarrhea (n = 12), abdominal pain (n = 8), and abdominal distention (n = 5). PLE was confirmed by fecal α1-AT clearance and/or Tc 99m human serum albumin scintigraphy. Hypoproteinemia was defined as a total protein value of < 6.0 g/dL or albumin value of < 3.0 g/dL. Fecal α1-AT was measured using radial immunodiffusion with a monospecific antiserum against α1-AT as described by Florent et al.[9] Sera and 3-day feces were taken and kept frozen until assayed. Feces were usually diluted at one-third volume in isotonic sodium chloride and then agitated for 60 minutes. After centrifugation at 3000 rpm for 20 minutes, the supernatant was assayed. Values indicative of PLE were α1-AT clearance > 13 mL/d. Tc 99m human serum albumin scintigraphy was performed every 3 minutes until 1, 2, 6, and 24 hours after injection. As overt gastrointestinal bleeding can show false positivity at both of these examinations, patients with overt bleeding were excluded. Of these 25 patients who underwent DBE, 23 patients underwent Tc 99m human serum albumin scintigraphy, in which abnormalities were detected in 19 (83%); and 18 patients underwent fecal α1-AT clearance, in which abnormalities were detected in 18 (100%). The median follow-up period after the first DBE was 16 months (range, 1 to 67 mo). This study was reviewed and approved by the Institutional Review Board of Nagoya University School of Medicine. Informed consent was obtained from all patients.

DBE, FCE, and VCE

DBE,[10,11] FCE,[12] and VCE (PillCam SB, Given Imaging Ltd., Yokneam, Israel or Endocapsule, Olympus Medical Systems Corp., Tokyo, Japan)[13] were performed as described previously. Briefly, FCE was performed with 200 to 400 mL of barium sulfate suspension through nasoenteric tube, and intermittent palpation and fluoroscopic evaluation performed until the terminal ileum was visualized. Next, air was insufflated into the small bowel with a nasoenteric tube to produce a double contrast effect.

Histologic Analysis

Bioptic specimens at DBE were reviewed histologically. Specific pathologic findings included dilated lymphatic lacteals in the lamina propria, immunopositive with a monoclonal antibody against D2-40 (Dako, Tokyo, Japan) in intestinal lymphangiectasia; amorphous eosinophilic substance that stained with Congo red in intestinal amyloidosis, which was subclassified by Congo red stain after incubation in potassium permanganate and immunostaining with the following antibodies: serum amyloid A (Dako; clone mc1), κ and λ light chains of the immunoglobulins (Dako; polyclonal), and β2-microglobulin (Dako; polyclonal); tumor cells in primary or metastatic small intestinal tumors; parasite bodies in strongyloidiasis; and granulomas in Crohn's disease.

Interpretation of Findings

Findings that could explain the symptoms of the patient and resulted in a change in therapeutic management were considered diagnostically positive. In patients with intestinal lymphangiectasia, FCE images including diffuse smooth nodular protrusions and thickening of the mucosal folds without ulceration and enteroscopic images including diffuse white plaques and white-tipped villi were positive. Final diagnoses were made using a combination of FCE, VCE, DBE, and the other modalities including pathology, if any, and the diagnostic yield was calculated.

Statistical Analysis

The proportions of patients with diagnostic yields at DBE with pathologic findings, FCE, and VCE were compared, and significant difference between the 2 tests was calculated by using the exact McNemer test. Comparison of diagnostic yields between ulcerative diseases and nonulcerative diseases was assessed by the Fisher exact test. Differences were considered significant with P values < 0.05.

RESULTS

Diagnosis of DBE, FCE, and VCE for PLE

We performed 47 DBE examinations (23 through the oral approach and 24 through the anal approach) in 25 patients with PLE and 15 FCE examinations in 15 patients. In 17 patients without intestinal obstruction at CT, DBE, or FCE, 19 VCE examinations were performed. Total enteroscopy at DBE was achieved in 3 patients, and it was not tried in 20 patients because diagnosis was obtained without total enteroscopy and in 2 patients who were not in good condition. Final diagnosis and clinical characteristics of these patients are presented in Table 1 and fecal α1-AT clearance stratified by underlying disorders is shown in Figure 1. Serum globulin levels in small-bowel tumor from colonic adenocarcinoma, amyloid A protein (AA)-type intestinal amyloidosis secondary to rheumatoid arthritis, strongyloidiasis, and Crohn's disease were 3.0 g/dL or higher, which suggests complicating infection or chronic inflammation, unrelated to increased interstitial pressure. DBE including biopsies established a diagnosis in 7 of the 8 patients with intestinal lymphangiectasia (88%), 5 of 5 with chronic nonspecific multiple ulcers unrelated to nonsteroidal anti-inflammatory drugs of the small intestine (CNSU) (100%), 4 of 4 with intestinal amyloidosis (100%), 3 of 3 with small-bowel tumors (100%), 0 of 2 with extragastrointestinal diseases (0%), 1 of 1 with strongyloidiasis (100%), 1 of 1 with Crohn's disease (100%), and 1 of 1 with small-bowel ulcers due to polyarteritis nodosa (100%). Small-bowel tumors included diffuse-type mucosa-associated lymphoid tissue lymphoma (n = 1), human T-lymphotropic virus-1-associated adult T-cell lymphoma (n = 1), and metastatic small-bowel tumor from colonic adenocarcinoma (n = 1). Intestinal amyloidosis was subclassified into AA-type in 3 cases and amyloid light chain protein (AL)-type in 1 case by DBE-directed biopsy. Three cases of intestinal lymphangiectasia were diagnosed only by DBE-directed biopsy, and another case of intestinal lymphangiectasia was not diagnosed at any small-bowel examination until pathologic diagnosis at autopsy. Two patients with extragastrointestinal diseases were negative at all small-bowel examinations and at autopsy, and finally clinically suspected. One of these 2 patients had chronic right-sided heart failure. Her medical history included implantation of a permanent pacemaker at age of 11 due to complete atrioventricular block and tricuspid valve replacements at ages of the 25 and 31 due to tricuspid regurgitation. The other had cirrhosis due to chronic viral hepatitis C. His medical history included

TABLE 1. Clinical Characteristics of 25 Patients With Protein-losing Enteropathy

Final Diagnosis	No.	Median Age (y)	Male/ Female	Mean (SD) TP Level (g/dL)	Mean (SD) Albumin Level (g/dL)	Mean (SD) Globulin Level (g/dL)	Location (No.)				
							Duodenum	Proximal Jejunum	Distal Jejunum	Proximal Ileum	Distal Ileum
Intestinal lymphangiectasia*	8	38 (range, 18-73)	6/2	3.4 ± 0.7	1.5 ± 0.6	1.9 ± 0.4	3	5	4	4	4
Chronic nonspecific multiple ulcers unrelated to NSAIDs	5	38 (range, 22-50)	1/4	4.3 ± 1.0	2.0 ± 0.9	2.3 ± 0.3	0	0	1	3	5
Intestinal amyloidosis	4	66.5 (range, 66-79)	3/1	4.7 ± 0.5	2.1 ± 0.6	2.6 ± 0.5	3	3	3	3	4
Small-bowel tumors†	3	69 (range, 30-70)	3/0	4.4 ± 1.2	1.7 ± 0.7	2.7 ± 1.1	1	1	2	2	2
Extragastrointestinal diseases‡	2	50.5 (37, 64)	1/1	3.9 ± 0.5	1.9 ± 0.0	2.0 ± 0.5	—	—	—	—	—
Strongyloidiasis	1	53	0/1	4.7	1.3	3.4	1	1	1	0	0
Crohn's disease	1	71	1/0	6.4	1.9	4.5	0	0	1	1	1
Small-bowel ulcers due to polyarteritis nodosa	1	40	0/1	4.7	2.1	2.6	0	0	0	0	1

*Primary intestinal lymphangiectasia (n = 7) and intestinal lymphangiectasia secondary to macroglobulinemia (n = 1).
†Diffuse-type mucosa-associated lymphoid tissue lymphoma (n = 1), human T-lymphotropic virus-1-associated adult T-cell lymphoma (n = 1), and metastatic small-bowel tumor from colonic adenocarcinoma (n = 1).
‡Cirrhosis after living donor liver transplantation (n = 1) and congestive heart failure (n = 1).
NSAIDs indicates nonsteroidal anti-inflammatory drugs; TP, total protein.

bleeding from the esophageal varices followed by living donor liver transplantation at age of 62. He was diagnosed as PLE 2 years after transplantation. The overall diagnostic yield of DBE was 88% in 25 patients. In 15 patients who underwent both DBE and FCE, the detection rate of abnormalities of DBE was 100%, whereas that of FCE was 60% ($P = 0.041$). FCE failed to detect abnormalities in 3 patients with intestinal lymphangiectasia, 1 with metastatic small-bowel tumor, 1 with strongyloidiasis, and 1 with small-bowel ulcers due to polyarteritis nodosa. The detection rate of abnormalities of VCE was 76% in 17 patients without stricture and not significantly different with that of DBE (82%). VCE failed to detect abnormalities in 2 patients with intestinal lymphangiectasia and 2 with extragastrointestinal diseases. When CNSU, amyloidosis, small-bowel tumors, Crohn's disease, and small-bowel ulcers due to polyarteritis nodosa were classified into ulcerative diseases and intestinal lymphangiectasia, strongyloidiasis, extragastrointestinal diseases were classified into nonulcerative diseases, the diagnostic yields of FCE, VCE, and DBE for ulcerative diseases versus nonulcerative diseases were 70% (7/10) versus 25% (1/4; $P = 0.245$), 100% (7/7) versus 70% (7/10; $P = 0.228$), and 100% (14/14) versus 73% (8/11; $P = 0.071$).

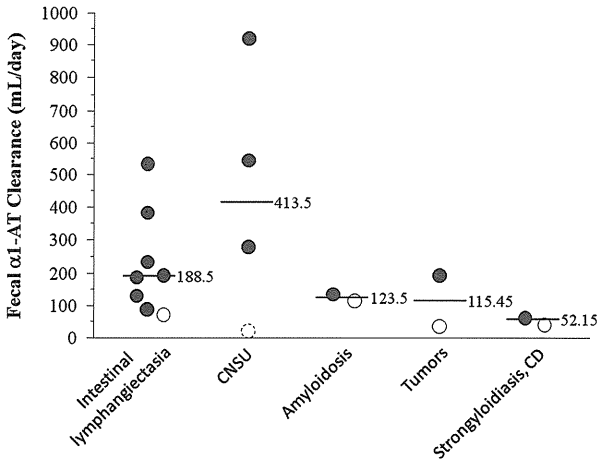

FIGURE 1. Fecal α1-AT clearance (normal ≤13 mL/d) stratified by underlying disorders. Closed circles indicate cases with positive technetium 99m human serum albumin scintigraphy. Open circles indicate cases with negative scintigraphy. The dotted open circle indicates a case without scintigraphy performed. The horizontal bars and numbers indicate the median value of fecal α1-AT clearance. AT indicates antitrypsin; CD, Crohn's disease; CNSU, chronic nonspecific multiple ulcers unrelated to NSAIDs of the small intestine; NSAIDs: nonsteroidal anti-inflammatory drugs.

Diagnosis of Other Preceding Examinations for PLE and Diagnostic Algorithm

Of 25 patients with PLE, 24 underwent EGD, in which abnormalities associated with PLE were detected in 4 (17%); and 25 underwent colonoscopy including terminal ileoscopy, in which abnormalities associated with PLE were detected in 3 (12%). Intestinal lymphangiectasia secondary to macroglobulinemia (n = 1), AA-type amyloidosis (n = 1), AL-type amyloidosis (n = 1), and strongyloidiasis (n = 1) were diagnosed at EGD and/or colonoscopy