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Short Communication

Utility of Combined Use of Transabdominal Ultrasonography and Fecal Immunochemical Test Examinations in Ulcerative Colitis

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This study examined the utility of the combined use of transabdominal ultrasonography (TUS) and fecal immunochemical testing (FIT) to detect mucosal inflammation, vis-a-vis the Mayo endoscopic subscore (MES), in ulcerative colitis (UC). Sixty-three UC patients who underwent TUS and FIT were retrospectively enrolled. For TUS, the colon was divided into five segments, and the bowel wall thickness was measured and evaluated. The accuracy of FIT (>100 ng/ml) in detecting mucosal inflammation (MES>0) was 0.93, whereas that of TUS (BWT>2 mm) in each segment was 0.84-0.97. The combined use of TUS and FIT may be helpful in noninvasive treatment strategies.

Key words: transabdominal ultrasonography, fecal immunochemical test, ulcerative colitis, Mayo endoscopic subscore

Ulcerative colitis (UC) is an intractable disease of unknown etiology that causes chronic inflammation of the gastrointestinal tract. This disease affects the colon and rectum, and there is no curative treatment; therefore, lifelong monitoring is required [1,2]. Colonoscopy is the standard evaluation method for UC [3]; however, because it is highly invasive, frequent examinations are difficult [4]. Therefore, accurate noninvasive exam modalities are needed to evaluate disease activity in patients with UC.

Evaluations of biomarkers in serum and stool are representative noninvasive examinations that have recently been the subject of many studies in the field of inflammatory bowel disease (IBD) [5-8]. Biomarkers include C-reactive protein and leucine-rich alpha-2 glycoprotein in the serum, as well as fecal calprotectin and the fecal immunochemical test (FIT). The advantage of biomarkers is that they can be measured easily with little variation; however, they primarily reflect the presence or absence of inflammation and do not provide more complex information, such as the extent, severity, or location of inflammatory lesions. Therefore, a combined examination that can provide complementary information may be ideal for disease evaluation in UC.

Transabdominal ultrasonography (TUS) is a noninvasive technique for real-time evaluation of the intestinal tract. TUS can be used to determine the presence or absence of inflammation and the extent, severity and location of inflammatory lesions in UC [9-13]. Therefore, TUS is expected to provide complementary information that will be useful for the treatment of UC.

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Among the biomarkers used in IBD clinical practice, our laboratory previously reported the usefulness of FIT, a stool marker, in UC [5-7]. This study examined the clinical utility of the combined use of TUS and FIT in UC management.

Materials and Methods

Patients. Patients with UC who visited the Okayama University Hospital between 2016 and May 2022 were included in this study. The availability of colonoscopy, TUS, and FIT measurements taken within 14 days was a criterion for inclusion, regardless of the order of these examinations. However, we did exclude patients who exhibited aggravation or improvement in clinical status due to changes in treatment between these examinations, as well as those under 15 years of age and those with a proctitis phenotype. All patients had an established diagnosis of UC based on endoscopic and histological assessment findings and had received medical therapy.

TUS. Aplio XG and Aplio 500 TUS machines (Cannon Medical Systems Corp., Ohtawara, Japan) were used to obtain TUS measurements in this study. Two doctors with three and six years of experience in TUS performed the procedures after at least five h of fasting. In some cases, previous endoscopic findings were used as references for determining disease activity and extent. In this study no preparations were used in performing TUS. A 7.5-MHz high-frequency linear-array transducer was used for evaluation. Each part of the colon was sequentially assessed, except for the rectum, which is difficult to visualize using TUS due to its location deep in the pelvis [10, 11]. The colon was divided into five segments: the ascending colon, right- and left-sided transverse colons, descending colon, and sigmoid colon. We measured bowel wall thickness, defined as the distance from the central hyperechoic line of the lumen (*i.e.*, the lumen of the digestive tract) to the outer hyperechoic margin of the wall (the serosa of the digestive tract), using a 7.5-MHz high-frequency linear-array transducer. Based on our previous report, we defined mucosal inflammation as a bowel wall thickness > 2 mm (Fig. 1) [12].

Colonoscopy. On the day of CS, the patients underwent a polyethylene glycol–based bowel preparation according to the manufacturer's instructions. Patients underwent colonoscopy after a colonic lavage. To avoid the risk of disease deterioration in patients with severe disease, a possible range was determined using colonic intestinal lavage by enteroclysis. Four doctors with at least seven years of experience in performing colonoscopies performed the procedures.

We compared the range of endoscopic observations with the ultrasound findings. Patients were excluded if the colonoscopic examination was limited to the rectum. The status of mucosal inflammation in each segment of the colon was assessed using the Mayo Endoscopic Subscore (MES) classification [14]. Mucosal inflammation in any segment was defined as an MES > 0, and mucosal healing (remission) was defined as an MES of 0. The MES was determined by endosco-

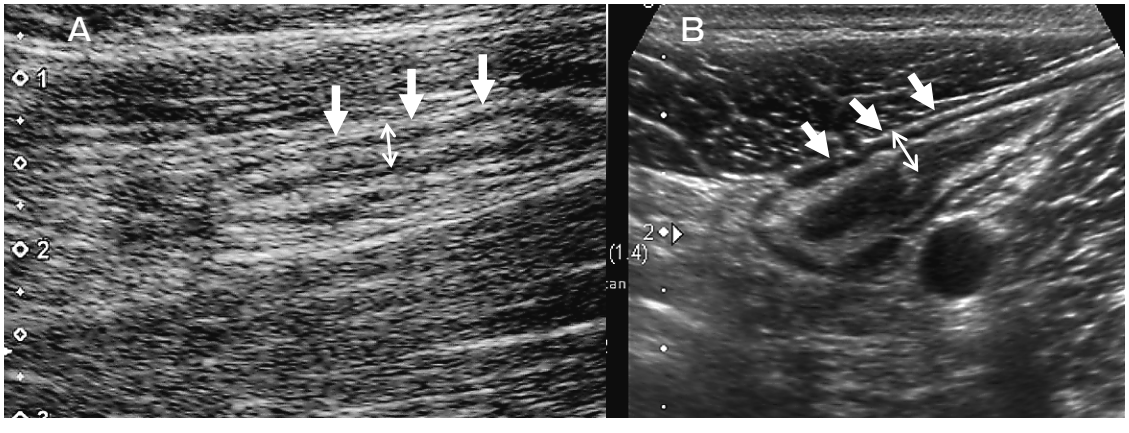

Fig. 1 US findings (sigmoid colon, 7.5 MHz). **A**, TUS findings of a bowel wall thickness of 1.5 mm (mucosa without inflammation); **B**, US findings of a bowel wall thickness of 3.7 mm (mucosa with inflammation). The sigmoid colon (white arrows) is indicated, along with the representative measurement method (two-headed white arrows). TUS, trans abdominal ultrasonography.

pists with > 10 years of experience, who were blinded to the TUS and FIT results. CS and TUS were performed by various physicians.

FIT analysis. The FIT analysis method has been described previously [5,6]. Fecal samples were prepared using a Hemodia sampling probe (Eiken Chemical, Tokyo, Japan). The stool samples were immediately processed and examined using an OC-Sensor DIANA (Eiken Chemical) system, which can accurately measure fecal hemoglobin at concentrations of 50-1,000 ng/ml. Fecal samples with hemoglobin concentrations greater than 1,000 ng/ml were diluted and then remeasured. Because FIT is not accurate for measuring hemoglobin concentrations < 50 ng/mL, specimens with hemoglobin concentrations within this range (0-50 ng/mL) were considered as 50 ng/ml. Based on our previous report [5,6], a FIT score > 100 was defined as positive.

Statistical analyses. All statistical analyses were conducted using JMP software version 13 (SAS Institute, Cary, NC, USA). The unaffected normal mucosa of left-sided colitis (transverse-ascending colon) was given an MES of 0. Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) with 95% confidence intervals (Cis) for detecting mucosal status were calculated using a 2×2 contingency table and determined based on TUS findings and FIT values. All p values were two-sided and considered significant at $p < 0.05$.

Statement of ethics. The study protocol was reviewed and approved by the Institutional Review Board of the Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences (approval number: 1804-030). All procedures were performed in accordance with the principles of the Declaration of Helsinki.

Results

Patient characteristics. A total of 63 patients with UC who underwent colonoscopy, TUS, or FIT testing within 14 days were enrolled in this study. The patient demographics and clinical characteristics are presented in Table 1. Most patients were men (70% [n = 44]) and had a pancolitis phenotype. All the patients underwent endoscopy to assess inflammation. Six patients were in remission with no inflammation in any segment. We refrained from examining the oral side of the colon when patients had high disease activity; therefore, the number of oral side evaluations was lower. Because rectal lesions are difficult to evaluate using TUS, we excluded patients with proctitis [10,11]. Nine patients underwent treatment changes during the examination; however, none showed a clear change in disease activity.

Sensitivity, ***specificity***, ***PPV***, ***and NPV of TUS and FIT for mucosal status***. Subsequently, we evaluated mucosal inflammation. Table 2 presents the sensitivity, specificity, PPV, NPV, and accuracy of TUS and FIT for each segment. Although the accuracy in the ascending colon was somewhat lower than that in the other segments, TUS was an excellent tool for detecting mucosal inflammation in each segment. FIT was also an excellent tool for detecting mucosal inflammation.

These results indicate that, although the number of remission states was somewhat low, both examinations were excellent in detecting mucosal inflammation, and TUS was useful in identifying the site of inflammation.

Table 1 Demographics and clinical characteristics of the study patients

Patients	
Total	63
Median age (range)	45 (16–85)
Median body mass index (range)	20.2 (12.3–30.0)
Gender	
Male	44 (70%)
Female	19 (30%)
Extent of disease	
pancolitis	51 (81%)
Left side coltis	12 (19%)
Evaluation site	
ascending colon	31 (49%)
right-sided transverse colon	34 (54%)
left-sided transverse colon	40 (63%)
descending colon	49 (78%)
sigmoid colon	63 (100%)
Endoscopic activity	
Remission states	7 (11%)
Active states	56 (89%)
Concomitant medications	
Aminosalicylate	47 (75%)
Corticosteroids	31 (49%)
Mercaptopurine/Azathioprine	16 (25%)
Biologics/JAK inhibitor	7 (11%)
Apheresis	12 (19%)
Tacrolimus	9 (14%)

Table 2 Sensitivity, specificity, and predictive values of TUS and FIT for mucosal inflammation, respectively (BWT > 2 mm, FIT > 100 ng/ml, MES > 0)

	S/C	D/C	T/C left	T/C right	A/C	FIT
Sensitivity	1.00 (0.96–1.00)	0.95 (0.89–0.97)	0.85 (0.76–0.85)	1.00 (0.85–1.00)	0.83 (0.62–0.94)	0.93 (0.89–0.93)
Specificity	0.82 (0.63–0.82)	0.90 (0.67–0.98)	1.00 (0.84–1.00)	0.84 (0.73–0.84)	0.84 (0.71–0.91)	1.00 (0.80–1.00)
PPV	0.96 (0.93–0.96)	0.97 (0.91–0.99)	1.00 (0.90–1.00)	0.83 (0.71–0.83)	0.77 (0.58–0.88)	1.00 (0.96–1.00)
NPV	1.00 (0.77–1.00)	0.82 (0.61–0.89)	0.78 (0.65–0.78)	1.00 (0.86–1.00)	0.89 (0.75–0.96)	0.64 (0.44–0.64)
Accuracy	0.97 (0.90–0.97)	0.94 (0.84–0.97)	0.90 (0.79–0.90)	0.91 (0.78–0.91)	0.84 (0.67–0.92)	0.94 (0.87–0.94)

TUS, transabdominal ultrasonography; FIT, fecal immunochemical test; BWT, bowel wall thickness; MES, Mayo endoscopic subscore; S/C, sigmoid colon; D/C, descending colon; T/C, transverse colon; A/C, ascending colon.

Discussion

UC is characterized by chronic inflammation of the gastrointestinal tract, and no radical treatment is currently available for it. Therefore, patients with this condition require lifelong management [1]. Colonoscopy is the standard disease assessment method for UC; however, it is invasive and may impose mental and physical burdens on patients, which can worsen their condition. Ideally, a noninvasive method that would be less burdensome for the patient could be used to assess relapse and disease activity. Serum and stool biomarkers, as well as imaging, are representative noninvasive examinations. This study investigated the utility of combining different noninvasive examinations, a stool biomarker (FIT) and an imaging modality (TUS), in evaluating UC.

Our results showed that FIT was very useful for identifying mucosal inflammation (MES > 0) throughout the colon while TUS was very useful in identifying mucosal inflammation segment by segment (MES > 0); in other words, TUS can identify the site of inflammation. Detecting the presence of inflammation and the site of inflammation can be expected to help assess and adapt the treatment strategy in a noninvasive manner. For example, if the inflammation is on the left side of the colon, local therapy can be used.

In this way TUS compensates for information not available with FIT. However, using TUS alone would present several limitations. First, evaluating rectal lesions using TUS is difficult. Recently, a method for evaluating ultrasound findings using a perineal approach has been reported [11], and the addition of such a method may provide a solution for rectal lesions. Another problem is that while the use of TUS to monitor UC is routine in Europe, this is not the case in Japan, resulting in a small number of adept practitioners and discrepancies in skills among facilities. By contrast, the FIT test is easy to perform and exhibits less variation in measured values. Therefore, serum and stool markers, including the FIT, tend to be used more frequently than TUS in managing UC. Based on the current situation, it is difficult to perform TUS regularly, and it is ideal to focus on the target group. Therefore, we believe that the best workflow for the positioning of both the FIT and TUS in UC practice is to perform TUS only if the FIT is positive.

This study has several limitations. First, the number of evaluations for each segment and degree of inflammation differed. To avoid this problem, one possible solution is to recruit patients whose entire colon can be observed using CS. Another limitation was that this was a retrospective study. Therefore, the examination period differed among the patients, and the examinations could not be completely blinded. A prospective study is underway to obtain reliable results. In addition, the possibility of inter-rater variability in TUS findings could not be ruled out; therefore, it seemed necessary to take countermeasures.

In conclusion, we demonstrated, for the first time, the potential utility of combining TUS and FIT in clinical management of UC. The relationship between the stool biomarker fecal calprotectin and TUS has been studied [15], and we believe that it is also significant that FIT was shown to be useful in our study.

Combining TUS and FIT in clinical practice can provide information on mucosal inflammation and the location of inflammation in specific bowel segments,

allowing the employment of targeted therapeutic approaches. We aim to clarify the relationship between these examinations and their use in clinical management of UC in future prospective studies.

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