

Evaluation of the Upper Gastrointestinal Tract in Ulcerative Colitis Patients

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To analyze the clinical characteristics of patients with ulcerative colitis who have upper gastrointestinal lesions, we retrospectively reviewed the data of 216 patients with ulcerative colitis who underwent esophagogastroduodenoscopy at our institute in April 2008-March 2016. We investigated the endoscopic features and compared the clinical characteristics between the patients with and without upper gastrointestinal lesions. Forty-two patients (19.4%) had upper gastrointestinal lesions, including multiple erosions (n=18), bamboo joint-like appearance (n=17), mucosa with white spots (n=4), friable mucosa (n=2), ulcer (n=1), and purulent deposits within the mucosa (n=1) in the stomach and/or duodenum. Compared to the patients without upper gastrointestinal lesions, those with upper gastrointestinal lesions showed significantly more frequent extraintestinal manifestations (19.0% vs. 8.0%, $p < 0.05$) and a significant history of colectomy (33.3% vs. 12.1%, $p < 0.01$). There were no significant differences with regard to the sex ratio, age at esophagogastroduodenoscopy, gastrointestinal symptoms, time since the diagnosis of ulcerative colitis, type of colitis at the initial diagnosis of ulcerative colitis, or gastric atrophy between the groups. In conclusion, gastroduodenal lesions were identified in 19.4% of the patients with ulcerative colitis. Esophagogastroduodenoscopy is particularly recommended for ulcerative colitis patients who show extraintestinal manifestations and for those who have undergone a colectomy.

Key words: ulcerative colitis, esophagogastroduodenoscopy, gastritis

Ulcerative colitis is an inflammatory bowel disease that causes inflammation in the digestive tract. As the name “ulcerative colitis” implies, it has long been believed that the inflammatory response is localized in the large intestine. However, studies conducted over the last 20 years have led to advances in our understanding of the extent of the disease. Macroscopic and microscopic involvement of the stomach and duodenum in ulcerative colitis patients has been reported by

several research groups [1-7] as “gastroduodenitis associated with ulcerative colitis,” “ulcerative gastroduodenal lesions,” or “ulcerative colitis-associated upper gastrointestinal inflammation.” These lesions are reportedly observed as friable mucosa, granular mucosa, or multiple aphthae during esophagogastroduodenoscopy [7].

Due to the increasing frequency of ulcerative colitis in developed countries since the mid-20th century, ulcerative colitis patients have been treated at various institutions ranging from tertiary care centers and com-

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munity hospitals to clinics. One of the concerns in treating ulcerative colitis is that the upper gastrointestinal involvement may be overlooked because of the lack of recognition of the gastroduodenal lesions by the attending physician. In addition, since the clinical backgrounds of patients with ulcerative colitis-associated upper gastrointestinal inflammation have not been fully revealed, no criteria have been established to indicate which patients should undergo esophagogastroduodenoscopy.

Patients with ulcerative colitis-associated upper gastrointestinal inflammation may require specific treatment for the gastroduodenal lesions. Hence, recognition and detection of the upper gastrointestinal lesions are important. Here we describe 2 cases of ulcerative colitis and summarize the results of our investigation of the prevalence of upper gastrointestinal involvement detected by esophagogastroduodenoscopy. We also analyzed the macroscopic and microscopic features of the upper gastrointestinal lesions and patient characteristics.

Methods

A database search performed at the Department of Gastroenterology and Hepatology of our institute identified 404 patients with ulcerative colitis who were treated at our institute between April 2008 and March 2016. Among them, 216 patients (53.5%) underwent one or more esophagogastroduodenoscopy examinations at our facility. Therefore, a total of 216 patients were enrolled in this study.

The presence or absence of esophageal, gastric, and duodenal lesions was macroscopically defined according to the results of the esophagogastroduodenoscopy examination(s). Atrophic gastritis, superficial gastritis, verrucous gastritis, single erosion, xanthoma, mucosal redness, candida esophagitis, esophageal hiatal hernia, hyperplastic polyp, fundic gland polyp, ulcer scar, reflux esophagitis, ectopic gastric mucosa, and varices were excluded from this study, since these lesions likely occur in no relation with ulcerative colitis. Verrucous gastritis is characterized by mucosal elevation with a central depression, which is usually multiple and arranged in chains or clusters in the antrum [8]. For the purposes of this paper, we defined all other lesions as upper gastrointestinal lesions because there is no consensus with regard to the definition of upper gastroin-

testinal involvement in ulcerative colitis to date [1].

Based on the presence of the upper gastrointestinal lesions, we divided the 216 patients into 2 groups: the patients with positive upper gastrointestinal lesions (the Lesion group) and the patients without upper gastrointestinal lesions (the No-Lesions group). We retrospectively reviewed the patients' endoscopic, radiological, biological, and pathological examination findings obtained from the clinical records of the patients. The patient information in the 2 groups was analyzed and compared with regard to sex, age at the esophagogastroduodenoscopy, time (years) since the diagnosis of ulcerative colitis, the presence or absence of gastrointestinal symptoms, the type of colitis (proctitis, proctosigmoiditis, left-sided colitis, and pan-ulcerative colitis) at the initial diagnosis of ulcerative colitis, the presence or absence of extraintestinal manifestations, history of surgery for ulcerative colitis, and gastric atrophy. Two board-certified endoscopists blindly assessed the grade of gastric atrophy according to the Kimura and Takemoto grading classification [9]. In cases of a difference of opinion between 2 endoscopists, the grade was determined after discussion.

Pathological features were analyzed when biopsy sampling was performed during an esophagogastroduodenoscopy examination. Lesions with focal enhanced gastritis or with aggregates of neutrophils and sloughed epithelial cells within a partially ruptured gastrointestinal gland that resemble crypt abscesses were defined as ulcerative colitis-associated upper gastrointestinal inflammation [10].

Our statistical analyses of the groups were performed with *t*-tests, chi-square tests, and F-tests using JMP 12.0.1 software (SAS, Cary, NC, USA). *P*-values < 0.05 were considered significant.

The study design was approved by the Ethics Committee of Okayama University Hospital (No. 1606-018), and it adhered to the Declaration of Helsinki.

Results

The patient backgrounds are summarized in Table 1. Among the 216 patients who underwent esophagogastroduodenoscopy, upper gastrointestinal lesions were identified in 42 (21 men and 21 women) patients (19.4%); these patients were classified as the Lesion group. The No-Lesions group was comprised of 174 patients (94 men, 80 women).

A comparison of the backgrounds of the patients in the 2 groups revealed that extraintestinal manifestations were observed significantly more frequently in the Lesion group (19.0%) compared to the No-Lesions group (8.0%, $p < 0.05$). The extraintestinal manifestations in the Lesion group included arthritis ($n = 2$), primary sclerosing cholangitis ($n = 2$), skin lesions (pyoderma gangrenosum, $n = 2$), stomatitis ($n = 1$), and ophthalmia (scleritis, $n = 1$). The extraintestinal manifestations in the No-Lesions group were arthritis ($n = 9$), primary sclerosing cholangitis ($n = 3$), and skin lesions ($n = 2$; one patient had erythema nodosum and the other had both pyoderma gangrenosum and erythema nodosum).

In addition, 33.3% of the patients in the Lesion group underwent surgery for ulcerative colitis, at a significantly higher rate than that in the No-Lesions group (12.1%, $p < 0.01$). There were no significant differences between patients in the Lesion and No-Lesions groups with regard to sex ratio (males: 50.0% vs. 54.0%), age

at esophagogastroduodenoscopy (mean \pm SD: 44.3 ± 19.6 vs. 45.0 ± 15.7 years), gastrointestinal symptoms (positive: 40.6% vs. 29.7%), time since the diagnosis of ulcerative colitis (mean \pm SD: 9.8 ± 9.9 vs. 8.1 ± 8.1 years), type of colitis at the initial diagnosis of ulcerative colitis (ratio of pan-ulcerative colitis: 59.5% vs. 49.4%), and gastric atrophy (ratio of C3, O1, O2, and O3: 14.4% vs. 13.8%), respectively.

Macroscopic features of the upper gastrointestinal lesions were classified as multiple erosions ($n = 18$), bamboo joint-like appearance ($n = 16$), mucosa with white spots ($n = 4$), friable mucosa ($n = 2$), ulcer ($n = 1$), and purulent deposits within the mucosa ($n = 1$). The typical images of each endoscopic feature are shown in Fig. 1. Table 2 shows the distribution of these features, which were observed in the stomach and duodenum. No patient had macroscopic lesions in the esophagus. One patient had mucosa with white spots along with a friable mucosa in the stomach. In 2 patients, the macroscopic features changed during the clinical course,

Table 1 Characteristics of the study subjects, 216 ulcerative colitis patients

	Lesion group	No-Lesions group	<i>P</i> -value
Total no. of patients	42	174	
Male	21	94	0.731
Female	21	80	
Age at the initial EGD (years, mean \pm SD)	44.3 ± 19.6	45.0 ± 15.7	0.815
Time since the ulcerative colitis diagnosis (years, mean \pm SD)	9.8 ± 9.9	8.1 ± 8.1	
Disease extent			
Pancolitis	25	86	0.302
Left-sided colitis, proctosigmoiditis, and proctitis	17	88	
Symptoms			
Present	13	38	0.289
Absent	19	90	
Not available	10	46	
Extraintestinal manifestations			
Present	8	14	0.046*
Arthritis	2	9	
Primary sclerosing cholangitis	2	3	
Skin lesions	2	2	
Stomatitis	1	0	
Ophthalmia	1	0	
Absent	34	160	
History of surgery for ulcerative colitis			
Present	14	21	0.002
Absent	28	153	

Lesion group: the patients with ulcerative colitis who had upper gastrointestinal lesions.

No-Lesions group: the patients without upper gastrointestinal lesions. *Present vs. absent.

EGD, esophagogastroduodenoscopy.

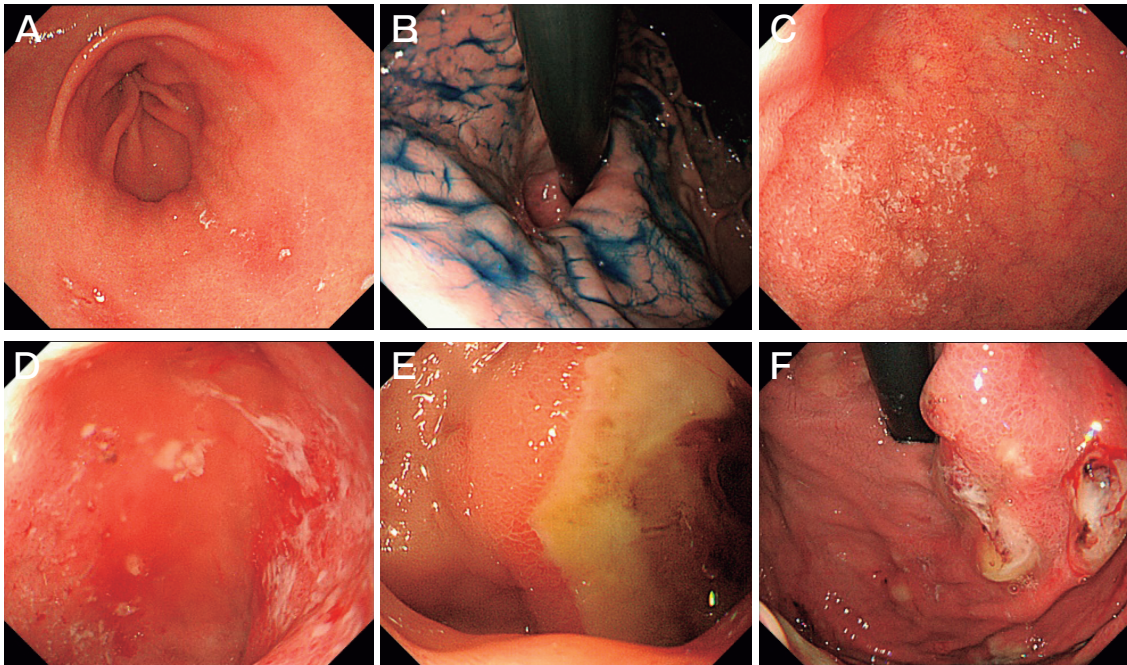


Fig. 1 Typical images of macroscopic features of the upper gastrointestinal lesions in patients with ulcerative colitis. Esophagogastroduodenoscopy revealed gastric multiple erosions (A), a bamboo joint-like appearance in the stomach (B), duodenal mucosa with white spots (C), duodenal friable mucosa (D), a duodenal ulcer (E), and purulent deposits within the gastric mucosa (F).

Table 2 Endoscopic features of the upper gastrointestinal lesions

Macroscopic feature	No. of patients	Stomach	Duodenum	Stomach and duodenum
Multiple erosions	18	13 [†]	4*	1
Bamboo joint-like appearance	17	17*	0	0
Mucosa with white spots	4	2	2	1
Friable mucosa	2	1 [†]	0	1
Ulcer	1	0	1	0
Purulent deposits within the mucosa	1	1	0	0

*Patient 1 presented with multiple erosions in the duodenum during the initial esophagogastroduodenoscopy (EGD), whereas the second EGD showed a bamboo joint-like appearance in the stomach.

[†]In Patient 2, gastric lesions were observed as mucosa with white spots at the initial EGD. The gastric lesions changed into multiple erosions at the second EGD.

and are described below. All other patients showed a single type of macroscopic feature on esophagogastroduodenoscopy. The detailed medication histories of the patients in the Lesion group were further investigated, revealing that during esophagogastroduodenoscopy, nonsteroidal anti-inflammatory drugs (NSAIDs) were prescribed for only one patient in whom an ulcer was identified.

Biopsy sampling was performed in 18 patients from the Lesion group. Focally enhanced gastritis was identified in 3 patients; 2 patients had multiple erosions and

the third patient had bamboo joint-like appearance. No crypt abscess was found in any of the biopsied specimens. Consequently, the 3 patients were diagnosed with ulcerative colitis-associated upper gastrointestinal inflammation [9].

Among the 15 patients without focally enhanced gastritis, nonspecific inflammation within the mucosa and submucosa was identified in 11 patients, and an intact gastric mucosa lacking inflammation was observed in three patients. In these three patients, biopsy sampling was performed for the bamboo joint-

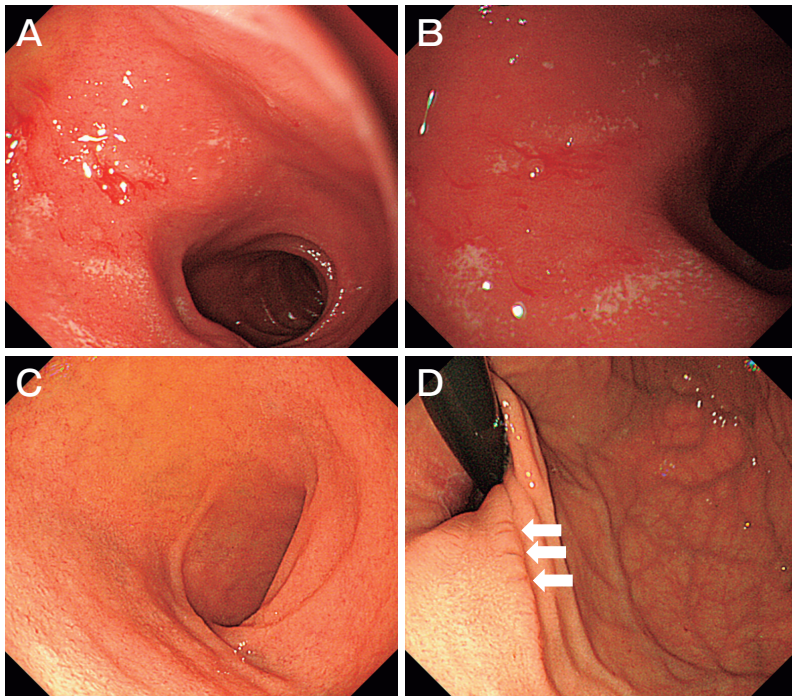


Fig. 2 Endoscopy images of Patient 1. Multiple erosions were initially observed in the duodenum (A,B). After the administration of mesalazine powder, the duodenal erosions resolved (C). A bamboo joint-like appearance appeared in the gastric cardia (D).

like appearance. In the remaining patient, since the samples were obtained from the purulent deposits within the mucosa, the pathologic features could not be evaluated due to the small volume of the sample.

Based on the results of an esophagogastroduodenoscopy examination, specific treatment for the upper gastrointestinal lesions was initiated in 2 patients. The clinical courses of these 2 patients are as follows.

Case 1. A 26-year-old Japanese woman was diagnosed with ulcerative colitis. When she was 27 years old, subtotal proctocolectomy was performed based on the deterioration of colitis. At 32 years of age, the patient underwent esophagogastroduodenoscopy for the investigation of epigastralgia, which revealed multiple erosions in the duodenum (Fig. 2A,B). Powdered mesalazine was administered to treat the duodenal lesions. When the patient was 35 years old, esophagogastroduodenoscopy revealed resolution of the duodenal erosions (Fig. 2C) and a bamboo joint-like appearance was noted in the gastric cardia (Fig. 2D); this appearance had not been identified during the initial esophagogastroduodenoscopy.

Case 2. A 14-year-old Japanese boy was diagnosed with ulcerative colitis. He underwent subtotal proctocolectomy at 17 years of age. Esophagogastroduodenoscopy performed at 19 years revealed white

spots in the gastric body (Fig. 3A), whereas the gastric antrum seemed to be intact (Fig. 3B). The patient was treated with powdered mesalazine. Esophagogastroduodenoscopy performed 1 year later showed reddish mucosa in the gastric body (Fig. 3C) and multiple erosions in the gastric antrum (Fig. 3D, E).

Discussion

In this study, 42 of the 216 patients (19.4%) who underwent esophagogastroduodenoscopy had upper gastrointestinal lesions. Horii *et al.* prospectively performed esophagogastroduodenoscopy with biopsies on 250 patients with ulcerative colitis. They identified ulcerative colitis-associated upper gastrointestinal lesions, which were defined as friable mucosa, granular mucosa, or multiple aphthae, in 7.6% of the patients [7]. Abnormalities in macroscopic findings have been identified in 13-53% of patients with ulcerative colitis [7]. Horjus Talabur Horje *et al.* reported that no patient with ulcerative colitis had upper gastrointestinal lesions, whereas macroscopic abnormalities were found in 41% of patients with Crohn's disease during esophagogastroduodenoscopy [11]. Such diversity of prevalence likely reflects the difference in the definition of upper gastrointestinal lesions among the different studies. Several

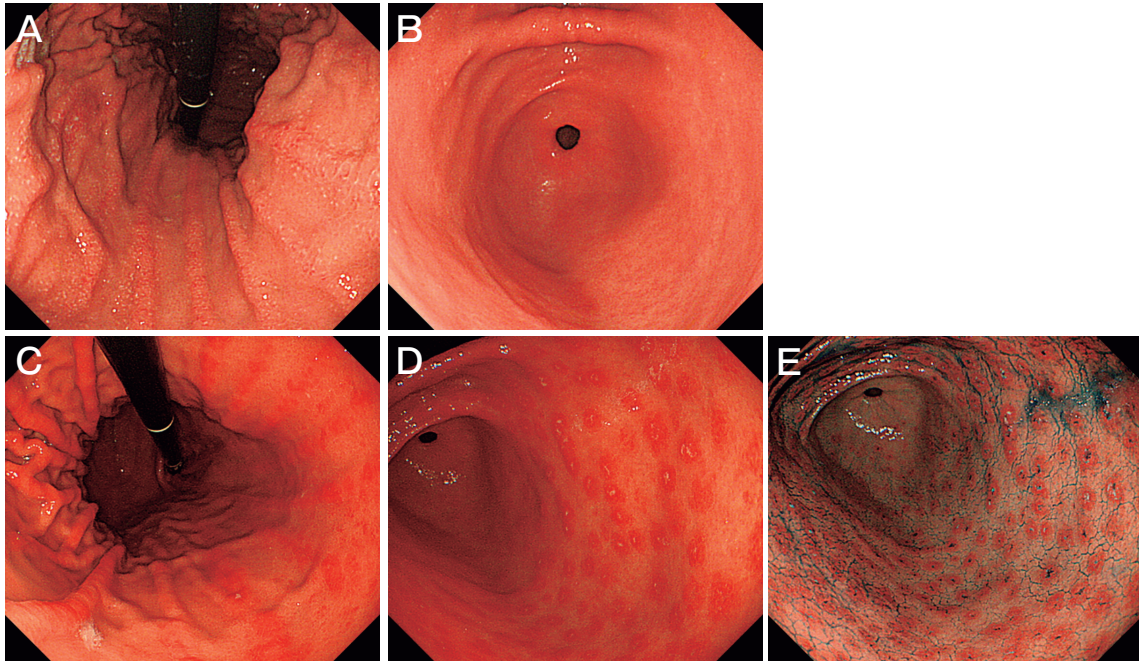


Fig. 3 Endoscopy images of Patient 2. White spots were observed in the gastric body (A), whereas the gastric antrum was intact (B). The patient was treated with powdered mesalazine. The second esophagogastroduodenoscopy revealed reddish mucosa in the gastric body (C) and multiple erosions in the antrum (D, E).

studies have revealed that a significant proportion of patients have macroscopic lesions in the upper gastrointestinal tract, indicating the importance of esophagogastroduodenoscopy examinations in the management of ulcerative colitis.

As we noted above, there is no consensus regarding the definition of upper gastrointestinal involvement in ulcerative colitis to date. In one prospective study, granular, erythematous mucosa, erosions, ulcers, nodular lesions and strictures were assessed as upper gastrointestinal lesions [11]. In a retrospective study, granular mucosa, erosion, mucosal friability, bleeding, and ulcers resembling colonic lesions, were classified as upper gastrointestinal lesions [12]. In the majority of studies, as well as in our present investigation, lesions were defined based on the macroscopic features.

Lin *et al.* pathologically investigated the upper gastrointestinal mucosa and defined ulcerative colitis-associated upper gastrointestinal inflammation as lesions with focal enhanced gastritis or with aggregates of neutrophils and sloughed epithelial cells within a partially ruptured gastrointestinal gland, resembling a crypt abscess [10]. This variation in the definitions reflects the difficulty of determining the lesions that actually occur

in relation to ulcerative colitis. In the present study, we included all mucosal alterations in the upper gastrointestinal tract other than atrophic gastritis, superficial gastritis, verrucous gastritis, single erosion, xanthoma, mucosal redness, candida esophagitis, esophageal hiatal hernia, hyperplastic polyp, fundic gland polyp, ulcer scar, reflux esophagitis, ectopic gastric mucosa, and varices. As a result, we identified multiple erosions, mucosa with white spots, friable mucosa, bamboo joint-like appearance, purulent deposits within the mucosa, and ulcers. Among these, ulcer formation might occur as an adverse effect due to NSAID use. In contrast, mucosa with white spots and friable mucosa have been reported as findings specific to ulcerative colitis [7]. Multiple erosions are also reportedly indicative lesions of upper gastrointestinal involvement with ulcerative colitis, provided other disorders such as viral infections, collagen, allergic, autoimmune, and Crohn's disease are excluded [7]. The significance of purulent deposits, which we observed in one patient, remains unknown, since the pathological analysis of the biopsied specimen was not possible due to the small sample size.

The bamboo joint-like appearance of the gastric

mucosa (*i.e.*, swollen longitudinal folds transversed by erosive fissures or linear furrows that are most frequently found at the gastric body and cardia) is a typical manifestation of Crohn's disease. It is well known that 44-65% of patients with Crohn's disease show a bamboo joint-like appearance of the gastric mucosa [13,14]. Recent reports on endoscopic gastroduodenal findings in patients with inflammatory bowel disease revealed that patients with ulcerative colitis have this feature [11,12,14]. In the present study, the bamboo joint-like appearance was found in 17 of the 216 patients (7.9%). Our finding reinforces the notion that the bamboo joint-like appearance of the gastric mucosa can be seen in patients with ulcerative colitis as well as in those with Crohn's disease.

In our study, extraintestinal manifestations were more frequently observed in the patients with positive upper gastrointestinal lesions. Moreover, the Lesion group included a higher percentage of patients who had undergone colectomy. The reported risks for developing upper gastrointestinal lesions include more extensive colitis, a lower dose of prednisolone, the presence of pouchitis, post-colectomy status, and a longer post-operative period [7,11,16-22]. Although the precise mechanisms underlying the upper gastrointestinal lesions are unclear, several authors have speculated that immune response to the as-yet unidentified factors associated with ulcerative colitis may also be the cause, since patient characteristics that are suggestive of severe inflammation are reportedly related to gastroduodenal manifestations [1,2,5,23].

In the present study, the extent of colitis was not a significant factor in the development of upper gastrointestinal lesions. However, the type of colitis was defined at the initial diagnosis of ulcerative colitis, and information regarding the disease extent at the time of esophagogastroduodenoscopy examination was not available, since esophagogastroduodenoscopy and colonoscopy were performed at different time points in most of the patients. Although an evaluation of disease extent and activity may be useful to predict the presence of upper gastrointestinal lesions, further studies are required in this regard. Based on the results of the present study, we speculate that esophagogastroduodenoscopy is particularly recommended for patients with ulcerative colitis who show extraintestinal manifestations and in those who have undergone colectomy. Among the 188 patients with ulcerative colitis who had

never undergone esophagogastroduodenoscopy, 21 (11.2%) were in post-colectomy status. We thus intend to perform esophagogastroduodenoscopies in this patient population.

Pathologically, focally enhanced gastritis was identified in 3 patients. This feature represents intense focal inflammation characterized by localized collections of lymphocytes, neutrophils, and macrophages in the lamina propria [10]. Focally enhanced gastritis was originally described in patients with Crohn's disease by Oberhuber *et al.* in 1997 [24]. To date, this is the most common upper gastrointestinal inflammation in ulcerative colitis. Lin *et al.* reported that 29% of patients with ulcerative colitis had focally enhanced gastritis, whereas 9% of control patients had this feature. A 12-29% prevalence of focally enhanced gastritis was reported in ulcerative colitis [10, 25-27]. Crypt abscess, a pathological hallmark of the large intestine in ulcerative colitis, can be identified in the upper gastrointestinal tract as well. Hori *et al.* reported that crypt abscesses were observed significantly more frequently in the gastroduodenal mucosa of patients with ulcerative colitis than in controls [7]. However, none of the patients in the present study had a crypt abscess. Nonspecific inflammation within the mucosa and submucosa was also identified in 11 patients without focally enhanced gastritis. This observation is consistent with a report that nonspecific inflammation in the upper gastrointestinal tract is observed in 60-90% of patients with ulcerative colitis [5].

Upper gastrointestinal lesions in ulcerative colitis may be treated with steroids, leukocytapheresis, and/or peroral mesalazine powder [12]. Immunosuppression with cyclosporine, tacrolimus, or infliximab is likely to be the treatment of choice for upper gastrointestinal inflammation as well. In the present study, mesalazine powder was administered to 2 patients, and the macroscopic features of the upper gastrointestinal lesions were found to have changed after the administration of this drug. One possible explanation is that mesalazine powder contributed to the altered macroscopic features. Another hypothesis is that the patients' morphology simply changed with time. Since the change in morphology was observed in only 2 patients, further studies are required to determine the exact factor(s) that affect the morphology.

Our study has several limitations. It was a retrospective analysis. Since esophagogastroduodenoscopy

was indicated in each patient by his or her attending physician, the timing of the examination during the course of ulcerative colitis varied. At our institution, we perform esophagogastroduodenoscopy for almost all patients with ulcerative colitis who have symptoms related to the upper gastrointestinal tract. Moreover, we usually recommend that patients with ulcerative colitis undergo esophagogastroduodenoscopy at least once. However, 188 of the 404 patients with ulcerative colitis (46.5%) in our study had never undergone an esophagogastroduodenoscopy examination. It is likely that the number of patients who underwent esophagogastroduodenoscopy and the reason for esophagogastroduodenoscopy might have affected the prevalence of the upper gastrointestinal lesions.

Second, our institute is a tertiary care center, where patients with ulcerative colitis who show relatively severe inflammation are referred from primary and secondary care centers. Such a composition of patients might affect the prevalence of upper gastrointestinal lesions. Third, although *Helicobacter pylori* is a well-known pathogen that causes various mucosal alterations in the stomach, the status of infection was not examined in this study, and only the presence of atrophic gastritis was endoscopically evaluated. Therefore, the influence of *H. pylori* on the gastroduodenal features could not be precisely assessed. It is noteworthy that several studies reported a negative association between *H. pylori* infection and ulcerative colitis [28-30]. Further studies with detailed information on *H. pylori* infection status are required to determine the roles of this organism in the pathogenesis, disease extent, severity, and upper gastrointestinal involvement of ulcerative colitis.

In conclusion, macroscopic lesions on esophagogastroduodenoscopy were observed in 19.4% of the patients with ulcerative colitis. Esophagogastroduodenoscopy is particularly recommended for patients with ulcerative colitis who show extraintestinal manifestations and for patients who have undergone a colectomy.

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