Gastric focal neutrophil infiltration and wide duodenal gastric foveolar metaplasia are histologic discriminative markers for Crohn's disease and Behçet's disease

（胃の限局性好中球浸潤と十二指腸における広域な胃上皮化生はクローン病とベーチェット病の組織学的鑑別マーカーとなる）

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Abstract

Background/Aims: Behçet's disease (BD) with intestinal lesions and Crohn's disease (CD) share clinical features. However, no report has compared the two diseases with regard to lesions of the upper gastrointestinal tract (UGT). We aimed to evaluate endoscopic and histologic findings of UGT in CD and BD. ***Methods:*** We retrospectively assessed the endoscopic records and biopsy samples of 84 *Helicobacter pylori*-negative patients (50 CD, 34 BD). In duodenal samples, MUC5AC immunohistochemical analysis was performed to identify gastric foveolar metaplasia. ***Results:*** In endoscopic findings, bamboo joint-like appearance (17/50 CD, 0/34 BD) and erosions (14/50 CD, 2/34 BD) were significantly more frequent in CD gastric lesions ($p<0.001$, and $p=0.012$). In histologic findings of stomach, focal neutrophil infiltration in lamina propria (15/48 CD, 1/34 BD) was significantly more frequent in CD ($p<0.001$). In that of duodenum, wide gastric foveolar metaplasia (19/49 CD, 1/34 BD) was significantly more frequent in CD duodenal lesions ($p=0.013$). The mean maximum width of the gastric foveolar metaplasia was 1139.5±250.7 μm and 368.7±54.4 for CD and BD, respectively ($p=0.003$). ***Conclusions:*** In *H. pylori*-negative patients, gastric focal neutrophil infiltration and wide duodenal gastric foveolar metaplasia were important for distinguishing CD from BD.

Key Words: upper gastrointestinal tract・Crohn's disease・Behçet's disease・ histology・differential diagnosis

Abbreviations

BD	Behçet's disease
BJA	Bamboo joint-like appearance
BSAS	Behçet’s Syndrome Activity Score
CD	Crohn’s Disease
CDAI	Crohn’s Disease Activity Index
FEG	focally enhanced gastritis
IBD	inflammatory bowel disease
PPI	proton pump inhibitor
UGT	upper gastrointestinal tract

Introduction

Crohn's disease (CD) lesions occur throughout the intestinal tract and are typically transmural. These lesions lead to stenosis, perforation, or fistulas. Histopathologic legions of the upper gastrointestinal tract (UGT) are found in 64–90% of CD patients [1]. With regard to histologic findings of the stomach, the prevalence of characteristic findings such as epithelioid cell granuloma is relatively low, being 9–10.9% in CD patients [2, 3], and the incidence of focally enhanced gastritis is 10.5–76% [4-6]. In the duodenum, focal neutrophil infiltration has been reported as a diagnostic characteristic of CD [3].

Behçet's disease (BD) is an idiopathic systemic disease characterized by recurrent oral ulceration, genital ulceration, uveitis, and skin lesions. Patients with Mediterranean BD have gastrointestinal involvements ranging from 0–5% but in East Asia, gastrointestinal involvement is found in 5–25% of BD patients [7]. Therefore, in the East Asian region, BD is an important disease requiring differentiation from inflammatory bowel disease (IBD). Similar to CD lesions, BD-associated lesions occur throughout the gastrointestinal tract, with ileocecal lesions most frequently manifested [8, 9]. Although esophageal ulcers have been reported in several BD studies [10-12], a detailed and systematic characterization of gastroduodenal lesions is not yet available. Particularly, there is no report about the histopathological examination of gastroduodenal lesions in BD patients.

Our study aimed to conduct a detailed comparison of the endoscopic and histologic findings of UGT in CD and BD patients and to identify markers that are useful for differentiating between the two diseases.

Methods

Patients

We retrospectively reviewed the endoscopic records and biopsy samples of CD and BD patients who were examined between September 2008 and March 2016 at the Hirosaki University Hospital and six related facilities.

Patients Characteristics

In total, 50 patients with CD and 34 patients with BD were included in our study. CD was diagnosed according to the Investigation and Research Committee for Intractable Inflammatory Bowel Disease criteria, organized by the Japanese Ministry of Public Welfare, as previously described [13, 14]. BD was diagnosed on the basis of the 2003 Behçet's Disease Research Committee of Japan criteria [15, 16]. Patients diagnosed as having complete, incomplete, and suspected BD were included in this study. *Helicobacter pylori*-positive patients were excluded. Data from patients' medical records, including age, sex, disease duration, Crohn's disease activity index (CDAI) [17], Behçet's Syndrome Activity Score (BSAS) [18], disease locations and behaviors of CD [19], clinical subtypes of BD [15, 16] and treatments were obtained.

UGT Endoscopy

The endoscopic UGT evaluations were performed by eight experienced endoscopists; these endoscopic records were reviewed by two expert IBD endoscopists.

Abnormal UGT endoscopy findings were defined as redness, erosion, aphthae, ulcer, bamboo-joint like appearance, and notched sign.

Mucosal biopsy samples were taken from the normal mucosa of the gastric antrum and corpus, duodenum, and additional specific macroscopic lesions.

UGT Histology and Immunohistochemical Analysis

Histologic diagnosis was reviewed by two blinded expert IBD pathologists. The presence of features of ulcer, erosion, intestinal metaplasia, edema, focally enhanced gastritis (FEG) defined by the presence of a perifoveolar or periglandular cellular infiltrate containing mononuclear cells and granulocytes, epithelioid granulomas, cryptitis, crypt abscess, and neutrophil infiltrate in the lamina propria was assessed via histological analysis. In addition, villous atrophy and gastric metaplasia were assessed on duodenal mucosal biopsy samples. Gastric foveolar metaplasia lacks the fundic glands and is distinguished from ectopic gastric mucosa on that point. In the present study, ectopic gastric mucosa was excluded from the histologic findings.

To determine the region of gastric metaplasia in the duodenum, an immunohistochemical analysis of MUC5AC was performed on the duodenal biopsy samples from 42 CD and 34 BD patients. We measured the maximum width of gastric metaplasia and compared the mean values for CD and BD.

Statistical Analysis

To compare patient characteristics and endoscopic and histologic findings between CD and BD patients, we used the Mann-Whitney U-test for continuous variables and Fisher's exact test for categorical variables and we used receiver operating characteristic (ROC) analysis to determine the cut-off values of maximum width of gastric foveolar

metaplasia. The area under the ROC curve (AUC) was used to choose a threshold value for each test parameter by maximizing the combination of sensitivity and specificity. All data of histological lesion were analyzed by multivariate logistic regression to estimate discriminative factors. To account for confounding factors, we used the Mantel-Haenszel test. *p*-values<0.05 were considered statistically significant. Statistical analyses and calculations were performed using IBM SPSS for Windows (version 19.0; Chicago, IL, USA).

Ethical Considerations

Institutional review board approval was obtained and informed consent was provided by all patients.

Results

Patients

Patient demographic and clinical characteristics are presented in Table 1. In CD patients, the mean age at endoscopic examination was 30 years (range 11-55) and 38 patients were male (76%). The mean disease duration was 62 months (range 0-369) and the mean CDAI was 166 (range 46-430). According to the Montreal classification of IBD, 2 patients were L1 (4%), 7 patients were L2 (14%) and 41 patients were L3 (82%), 30 patients were B1 (60%), 14 patients were B2 (28%), 6 patients were B3 (12%) and 25 patients had perianal disease. In BD patients, the mean age at endoscopic examination was 49 years (range 23-77) and 13 patients were male (38.2%). The mean disease duration was 66 months (range 0-243) and the mean BSAS was 10.5 (range: 2-40). According to the diagnostic criteria for BD, 5 patients were complete type (14.7%), 28 patients were incomplete type (82.4%) and 1 patient was suspected (2.9%). The mean age and ratio of female to

male patients were significantly higher in BD patients than in CD patients.

Endoscopic Findings

The endoscopic findings of the stomach are summarized in Table 2. The number of patients with findings was 35 in CD (70%) and 12 in BD (35.3%). Erosion was found in 14 patients with CD (28%) and in 2 patients with BD (5.9%) (p=0.012). BJA was found in 17 patients with CD (34%) but was not found in BD patients (p<0.001). Erosion and BJA were significantly more frequent in CD patients than in BD patients.

The endoscopic findings of the duodenum are summarized in Table 2. The number of patients with findings was 29 in CD (58%) and 12 in BD (17.6%). Erosion was found in 14 patients with CD (28%) and 1 patient with BD. Aphtha, open ulcer, ulcer scar, and notch-like appearance were not found in BD patients. Erosion and ulcer scar were significantly more frequent in CD than in BD patients (p=0.003 and p=0.039).

Histologic Findings

Biopsy samples from the stomach were obtained from 48 CD patients (86 samples) and 34 BD patients (64 samples). Thirty-four CD patients (72.3%) and 5 BD patients (14.7%) had findings. These findings are summarized in Table 3. FEG (Fig. 1) and granuloma were found in 9 (10.5%) and 2 (2.3%) biopsy samples, respectively, from CD patients; both were not found in BD patients. Focal neutrophil infiltration in lamina propria was found in 17 biopsy samples from CD patients (19.8%) and 1 biopsy sample from BD patients (1.6%). FEG and focal neutrophil infiltration in lamina propria were significantly more frequent in CD patients than in BD patients (p=0.010 and p<0.001).

Biopsy samples from the duodenum were obtained from 47 CD patients (93 samples) and 34 BD patients (71 samples). The findings of 40 CD patients (85%) and 25 BD patients (73.5%) are summarized in Table 3. Villous atrophy was found in 55 samples from CD patients (59.1%) and 27 biopsy samples from BD patients (38.0%). Gastric foveolar metaplasia was found in 28 samples from CD patients (29.0%) and 8 biopsies from BD patients (11.3%). Focal neutrophil infiltration in lamina propria was found in 29 (31.2%) and 23 (24.7%) samples from CD patients and 6 (8.5%) and 3 (4.2%) samples from BD patients. Villous atrophy, gastric foveolar metaplasia, and focal neutrophil infiltration in lamina propria were significantly more frequent in CD patients than in BD patients (p=0.006, p=0.003, and p<0.001).

We performed a MUC5AC immunohistochemical analysis to determine a region of gastric foveolar metaplasia in the duodenum (Fig. 2). On Hematoxylin and Eosin staining, the mean maximum width of the gastric foveolar metaplasia was 1139.5±250.7 μm in CD patients and 368.7±54.4 μm in BD patients (p=0.003, Fig. 1A and 1C, Table 4). Regarding the MUC5AC immunohistochemical analysis, the mean maximum width of the gastric foveolar metaplasia was 1290.4±249.3 μm in CD patients and 387.5±63.1 μm in BD patients (p<0.001, Fig. 1B and 1D, Table 4). A region of the gastric foveolar metaplasia in the duodenum became clear with the MUC5AC immunohistochemical analysis. The ROC curve showed that maximum gastric foveolar metaplasia width on HE stain cut-off value of 550 μm could predict the correct diagnosis of CD with 57.1% sensitivity, 87.5% specificity, 95.0% positive predictive value (PPV), 53.8% negative predictive value (NPV) and an area under the curve (AUC) of 0.607 (fig. 3). By applying these cut-off values, wide gastric foveolar metaplasia was found in 19

CD patients (38.7%) and 1 BD patients (2.9%). In a multivariate logistic regression model, focal neutrophil infiltration in lamina propria of gastric lesion and wide gastric foveolar metaplasia of dudenunal lesion (>550 μm) were independent discriminate markers between CD and BD (Table 5).

Correspondence between Histologic and Endoscopic Findings

The correspondence between histologic and endoscopic findings is shown in Tables 6 and 7. This result includes biopsy samples from patients who underwent endoscopy several times. In the stomach, the number of biopsy samples from the endoscopically normal mucosa was 74 in CD and 70 in BD. Thirty-six patients with CD (48.6%) and 13 with BD (18.6%) had histologic findings. FEG was found in 9 samples and 7 of them were taken from the endoscopically normal mucosa. In the duodenum, the number of biopsy samples from the endoscopically normal mucosa was 63 in CD and 67 in BD. Of these, 35 CD (64.9%) and 36 BD (53.7%) had some histologic findings. Gastric foveolar metaplasia was found in 41 samples and 15 of them were taken from the endoscopically normal mucosa.

Confounding Factors

We examined correlations between patients' background and histologic findings. There was no correlation between CDAI or BSAS and histologic findings. No correlation was found between all drugs (infliximab, adalimumab, mesalazine, steroid, non-steroidal anti-inflammatory drugs, and proton pump inhibitor [PPI]) and histologic findings. The frequency of PPI administration in BD patients

was significantly high compared to that in CD patients (Table 1). We tested whether PPI administration was associated with the frequency of duodenal gastric foveolar metaplasia using Pearson's chi-square test (Table 8). There was no correlation between PPI administration and the prevalence of duodenal gastric foveolar metaplasia (p = 0.172).

Discussion

To our knowledge, the present study is the first report to compare the endoscopic and histologic findings of UGT in CD and BD patients and to identify any specific or characteristic markers useful for differentiating between the two diseases. Our study revealed that endoscopic and histologic methods might be useful tools for determining specific findings helping to differentiate BD from CD in *H. pylori*-negative patients. Duodenal gastric foveolar metaplasia in CD was significantly more frequent and wider than in BD, suggesting that although segmental inflammatory lesions are observed in both CD and BD patients, the distribution of inflammation in CD is more wider than in BD.

A study compared the ileocolonoscopic findings in CD and BD patients [20]. The
typical findings of intestinal BD are one or a few round or oval ulcers in the ileocecal lesion. Conversely, typical findings of CD are longitudinal ulcers and a cobblestone appearance. However, various ulcers, such as small aphthous ulcers and irregularly shaped ulcers, can be detected. When the lower endoscopic findings are atypical, upper endoscopic findings can aid diagnosis. Nevertheless, no report has compared upper lesions of CD and BD. In the present study, the prevalence of endoscopic lesions in the stomach and duodenum of BD patients was

approximately 20% and 10%, respectively, and the major findings were redness and erosions. However, the prevalence of endoscopic lesions in the stomach and duodenum of CD patients was approximately 50% and 37%, respectively, and the major findings were erosions, aphtha, and BJA. BJA, considered to be one of characteristic findings of CD [21, 22], was observed in approximately 37% of CD patients but was not noted in BD patients. Regarding the difference from BD, BJA was considered an important finding. However the occurrence of BJA was not notably high [2, 23], making its use alone might be insufficient for differentiating between non-representative cases of CD and BD. From our analysis, abnormal findings of upper gastrointestinal endoscopy in BD patients were infrequent, as in a past report [24]. Therefore, it is more important to evaluate the comparison of biopsy samples.

Our present data showed that in the stomach of BD patients, the frequency of histologic findings was low (approximately 2%). However, FEG, thought to be a diagnostic marker of CD, was not found in the gastric mucosa of BD patients. Focal neutrophil infiltration in lamina propria was also significantly frequent in CD patients, compared with BD patients. Notably, FEG was detected in nine samples of CD patients, but seven of these were biopsies from the sites without abnormal endoscopic findings. These data indicate that the histologic evaluation of sites with normal endoscopic findings is important to distinguish between the two diseases and FEG and focal neutrophil infiltration in lamina propria might be discriminate factors to differentiate between CD and BD.

In the duodenum of BD patients, the frequency of histologic findings was high (approximately 40%) and the major findings were villous atrophy and inflammatory cell infiltrations. However, endoscopic

findings were observed in only 10% of BD patients. These results suggest that histologically minute focal inflammations without endoscopic lesions occurred in the duodenum of BD patients. Therefore, it seems necessary to obtain a biopsy from the duodenum, regardless of the presence of endoscopic lesions during upper endoscopy.

In this study, granuloma in the stomach biopsy was detected in two CD cases, but not in BD. In these results, as in previous reports [2, 3], identifying a granuloma has a high specificity but its rate of detection is low (2.3%), suggesting that it might not be a suitable discriminative marker for diagnosis in UGT.

The prevalence of *H. pylori*-negative duodenitis is rare in the general population, and previous reports showed that frequency of the *H. pylori*-negative duodenitis in general population was approximately 2-6% [25, 26, 27]. Previous reports showed that in contrast, *H. pylori*-negative duodenitis has been reported to be more frequent in IBD, particularly in CD [28]. In the present data, gastric foveolar metaplasia, cryptitis and focal neutrophil infiltration in lamina propria of duodenum were significantly frequent in CD patients, compared with BD patients. These results showed that *H. pylori*-negative duodenitis was significantly more frequent in CD patients than in BD patients.

In a multivariate logistic regression model, focal neutrophil infiltration in lamina propria of gastric lesion and wide gastric foveolar metaplasia of dudenunal lesion (>550 μ m) were independent discriminate markers between CD and BD. Based on these data, we proposed the histologic index to diffentiate between CD and BD. Fulfilling the two histologic index, the sensitivity and specificity for the diagnosis of CD were 57.1% and 87.5% respectively.

In addition, the frequency of gastric foveolar metaplasia was

independent of therapeutic drugs including PPI or disease activity, suggesting that gastric foveolar metaplasia could be one of the histological markers of the index to differentiate between CD and BD. The evidence of duodenal gastric foveolar metaplasia supports the presence of chronic inflammation and duodenal ulcer [29]. Previous reports have implicated a high acid output into the duodenum in the development of gastric foveolar metaplasia [30]. Duodenal inflammation is also associated with *H. pylori* infection. However, it has been reported that the development of duodenal gastric foveolar metaplasia cannot be explained by *H. pylori* infection or peptic disorders alone [31]. Our present data showed that a high prevalence of duodenal gastric foveolar metaplasia in CD patients compared with BD patients was not associated with *H. pylori* infection or PPI use. However, gastric lesions in CD patients were significantly frequent compared with BD patients. Therefore, increased acid exposure ascribed to gastric inflammation associated with CD in duodenum might cause gastric foveolar metaplasia of duodenum.

It is well known that gastric metaplasia is closely associated with ectopic fundic mucosa. Although it cannot be denied the acquired appearance by metaplasia, the gastric foveolar epithelium found in ectopic fundic mucosa was more likely to appear inherently with fundic glands. Therefore gastric foveolar metaplasia observed in CD and BD patients in this study might be different from that derived from ectopic fundic mucosa.

It has been reported that barrier dysfunction in the duodenum occurs in IBD [32, 33]. In CD patients, increased permeability due to loss of barrier function occurred in the mucosa of duodenum, and duodenitis might be caused by bacteria entry and neutrophilic infiltration,

chronically. Therefore, our results suggest that duodenal gastric foveolar metaplasia might be ascribed to a loss of barrier function of intestinal epithelial cells. It is suggested that the barrier dysfunction might be present in BD patients as well as CD patients. In the histopathological evidence of lower digestive tract lesions, a range of inflammation of the margin of ulcer in BD patients is smaller than that in CD patients. Our data showed that the lesions of duodenal gastric foveolar metaplasia in BD patients were very forcal and the lengths of duodenal gastric foveolar metaplasia in BD patients were significantly short compared with CD patients. These data suggested that very focal inflammation in BD patients might be characteristic and the mechanism causing gastric foveolar metaplasia of duodenum in BD might be different from that in CD.

Some limitations exist in the present study. First, the study was limited to only *H. pylori*-negative patients; thus, the examination of *H. pylori*-positive persons is necessary. In IBD, *H. pylori* infection is not notable; therefore, a comparison with the rate of BD infection is necessary. Second, the specific endoscopic and histologic UGT findings that are associated with BD are unclear. Future large-scale studies are necessary to examine markers that can help diagnose BD via endoscopy and histology. Lastly, our study was retrospective, with a small sample size. Although we recognize that BD is a rare disease, further investigations involving a larger number of patients are required.

In conclusion, the present study revealed that the histologic findings of wide gastric foveolar metaplasia of duodenum and gastric focal neutrophil infiltration in lamina propria are key markers for differentiating between CD and BD. The histologic assessment of biopsy samples is more important in cases wherein endoscopic findings

are absent. We suggest that the histopathologic assessment of UGT can help in the diagnosis of non-representative cases, which may not be confirmed using clinical manifestations and lower endoscopic examinations.

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Figure Legends

Fig 1. Focally-enhanced gastritis(original magnification ×20).

Fig 2. Gastric foveolar metaplasia in the duodenum. A: Hematoxylin and Eosin stain in Crohn’s disease (original magnification ×10). B: MUC5AC immunohistochemistry in Crohn’s disease (original magnification × 10). C: Hematoxylin and Eosin stain in Behçet's disease (original magnification × 10). D: MUC5AC immunohistochemistry in Behçet's disease (original magnification × 10).

Fig 3. Receiver operator curve for maximum width of the gastric foveolar metaplasia showing the diagnostic accuracy for distinguishing between CD and BD.

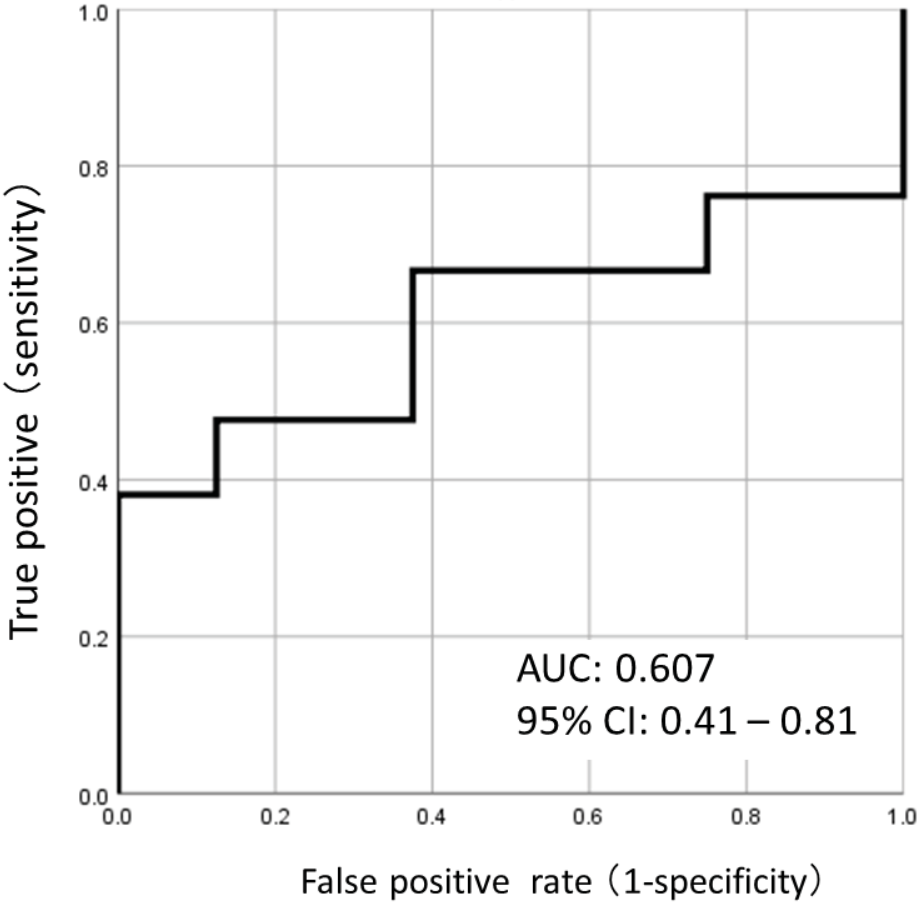

True positive（sensitivity）
1.0
0.8
0.6
0.4
0.2
0.0
0.0
0.2
0.4
0.6
0.8
1.0
AUC: 0.607
95% CI: 0.41 – 0.81
False positive rate（1-specificity）

TABLE 1. Patient characteristics and treatment

	CD (n=50)	BD (n=34)	p values
Age (mean±SD) (years)	30±3.5	48±3.8	<0.001
Male	38	13	<0.001
Disease duration (months)	62±10.5	66±8.5	0.051
CDAI	165.9±9.9	–	–
BSAS	–	10.5±3.4	–
Disease location of CD			
L1	2(4%)		
L2	7(14%)		
L3	41(82%)		
L4	0	–	–
Disease behavior of CD			
B1	30(60%)		
B2	14(28%)		
B3	6(12%)		
p	25(50%)		
Clinical subtype of BD			
complete	–	5(14.7%)	–
incomplete		28(82.4%)	
suspected		1(2.9%)	
Treatment			
Infliximab	9(18.0%)	6(17.6%)	0.576
Adalimumab	5(10.0%)	1(2.9%)	0.204
Mesalazin	26(60.5%)	3(9.1%)	<0.001
Steroid	5(11.4%)	9(27.3%)	0.072
NSAIDs	1(2.2%)	9(27.3%)	0.002
PPI	13(29.5%)	19(57.5%)	0.020

CD = Crohn's disease, BD = Behçet's disease, CDAI = Crohn's disease activity index,
BSAS = Behçet's Syndrome Activity Score, CNS = Central nervous system, GI = gastrointestinal
NSAIDs = Non-steroidal anti-inflammatory drugs, PPI = proton pump inhibitor

TABLE 2. Endoscopic findings

	CD (n=50)	BD (n=34)	p values
Stomach			
Redness	9(18.0%)	7(20.6%)	0.784
Aphtha	6(12.0%)	1(2.9%)	0.141
Erosion	14(28.0%)	2(5.9%)	0.012
Open ulcer	0	1(2.9%)	0.405
Ulcer scar	1(2.0%)	0	0.595
BJA	17(34.0%)	0	<0.001
Fundic gland polyp	0	11(32.3%)	<0.001
Duodenum			
Redness	6(12.0%)	3(8.8%)	0.467
Aphtha	1(2.0%)	0	0.595
Erosion	14(28.0%)	1(2.9%)	0.003
Open ulcer	5(10.0%)	0	0.069
Ulcer scar	6(12.0%)	0	0.039
Notched sign	2(4.0%)	0	0.267

CD = Crohn's disease, BD = Behçet's disease, BJA = bamboo joint-like appearance

TABLE 3. Histological findings

Stomach

	CD		BD		p values	
	48 patients	86 samples	34 patients	64 samples	patients	samples
Ulcer	0	0	0	0	—	—
Erosion	1(2.1%)	1 (1.2%)	0	0	0.585	0.573
Intestinal metaplasia	2(4.2%)	2 (2.3%)	0	0	0.340	0.327
Edema	3(6.3%)	3 (3.5%)	1(2.9%)	1 (1.6%)	0.447	0.428
FEG	8(16.7%)	9 (10.5%)	0	0	0.018	0.010
Granuloma	2(4.2%)	2 (2.3%)	0	0	0.340	0.327
Grands destruction by neutrophil infiltration	7(14.6%)	8 (9.3%)	0	0	0.019	0.010
Abscess	2(4.2%)	2 (2.3%)	0	0	0.340	0.327
Focal neutrophil infiltration in lamina propria	15(31.3%)	17 (19.8%)	1(2.9%)	1 (1.6%)	<0.001	＜0.001
Intraepithelial neutrophil infiltration	3(6.3%)	3(3.5%)	0	0	0.195	0.105

Duodenum

	CD		BD		p values	
	49 patients	93 samples	34 patients	71 samples	patients	samples
Ulcer	3(6.1%)	3 (3.2%)	1(2.9%)	1 (1.4%)	0.456	0.42
Erosion	2(4.1%)	2 (2.2%)	1(2.9%)	1 (1.4%)	0.636	0.601
Villous atrophy	40(81.6%)	55 (59.1%)	22(64.7%)	27 (38.0%)	0.123	0.006
Gastric foveolar metaplasia	25(51.0%)	28 (29.0%)	8(23.5%)	8 (11.3%)	0.013	0.003
Granuloma	1(2.0%)	1 (1.1%)	0	0	0.590	0.567
Cryptitis	10(20.4%)	11 (11.8%)	1(2.9%)	1 (1.4%)	0.023	0.009
Crypt abscess	0	0	0	0	—	—
Focal eutrophil infiltration in lamina propria	23(46.9%)	29 (31.2%)	4(11.8%)	6 (8.5%)	＜0.001	＜0.001
Intraepithelial neutrophil infiltration	11(22.4%)	13 (14.0%)	3(8.8%)	3 (4.2%)	0.089	0.060

CD = Crohn's disease, BD = Behçet's disease, FEG = focally enhanced gastritis

TABLE 4. Immunohistochemical analysis of MUC5AC for duodenal gastric foveolar metaplasia

Maximum length, μm mean±SE	CD (n=21)	BD (n=8)	p values
HE stain	1139.5±250.7	368.7±54.4	0.003
MUC5AC	1290.4±249.3	387.5±63.1	＜0.001

CD = Crohn's disease, BD = Behçet's disease, HE stain = Hematoxylin and eosin stain

TABLE 5. Predictor of CD

Histological lesion	Regression coefficient	Standard error	p values	Odds ratio (95% CI)
Focal neutrophil infiltration in lamina propria of stomach	2.444	1.098	0.026	11.5 (1.4-99.0)
Gastric foveolar metaplasia in duodenum(>550 μ m)	2.980	1.074	0.006	19.7 (2.4-161.4)

CI = Confidence interval

TABLE 6. Correspondence of histological findings with endoscopic findings in the stomach

	Endoscopic findings of biopsy samples from stomach									
	CD (118 samples)					BD (79 samples)				
Histological findings	Redness (9)	Erosion (15)	Aphtha (7)	BJA (13)	Normal (74)	Redness (4)	Erosion (3)	Aphtha (1)	Ulcer (1)	Normal (70)
Erosion		1								
Intestinal metaplasia		1	1							
Edema		1			3					1
Fibrosis		4		5	15	1		1		10
FEG	1	1			7					
Granuloma		1		1						
Grands destruction by neutrophil infiltration		5	1	1	2					
Abscess		2								
Neutrophil infiltration	2	8	3	2	6		2			1
Lymphocyte infiltration					10					
Eosinophil infiltration		1		1	1		1		1	
Plasma cell infiltration		2	1	2	8					1
Giant cell		1								
Vasodilation	4	1								
Intraepithelial neutrophil infiltration		2	1		1					

CD = Crohn's disease, BD = Behçet's disease, BJA = bamboo joint-like appearance, FEG = focally enhanced gastritis

TABLE 7. Correspondence of histological findings with endoscopic findings in the duodenum

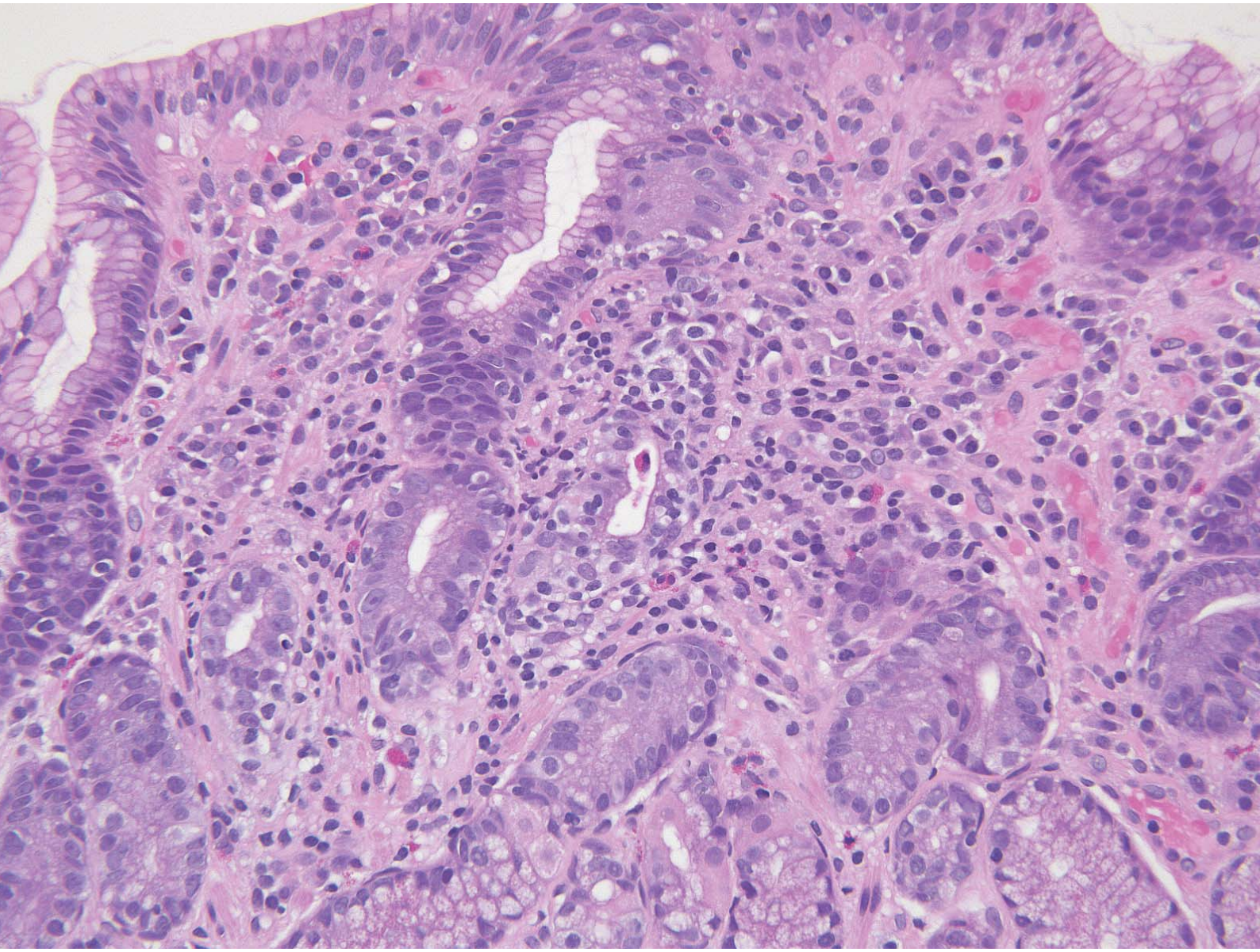
	Endoscopic findings of biopsy samples from the duodenum												
	CD (120 samples)								BD (85 samples)				
Histological findings	Redness (6)	Erosion (20)	Aphtha (1)	Ulcer (18)	VA (6)	GM (2)	NA (2)	Normal (63)	Redness (10)	Erosion (4)	White villous (3)	GM (1)	Normal (67)
Ulcer		2		1									
Erosion		2								1			
Villous atrophy	2	17	1	14	5	2	1	27	3	3	2		23
Edema		3		1						3	1		2
Fibrosis										1			1
Gastric foveolar metaplasia	1	10		8	3	2	1	8				1	7
Granuloma		2											
Cryptitis		10		4				1		3			
Neutrophil infiltration	2	15	1	9				10		3			5
Eosinophil infiltration	1	13		5		1		6	2	2	1		3
Plasma cell infiltration		11	1	6	2	1		8					3
Vasodilation				1							1		3
Intraepithelial neutrophil infiltration		8		8				3		2			2

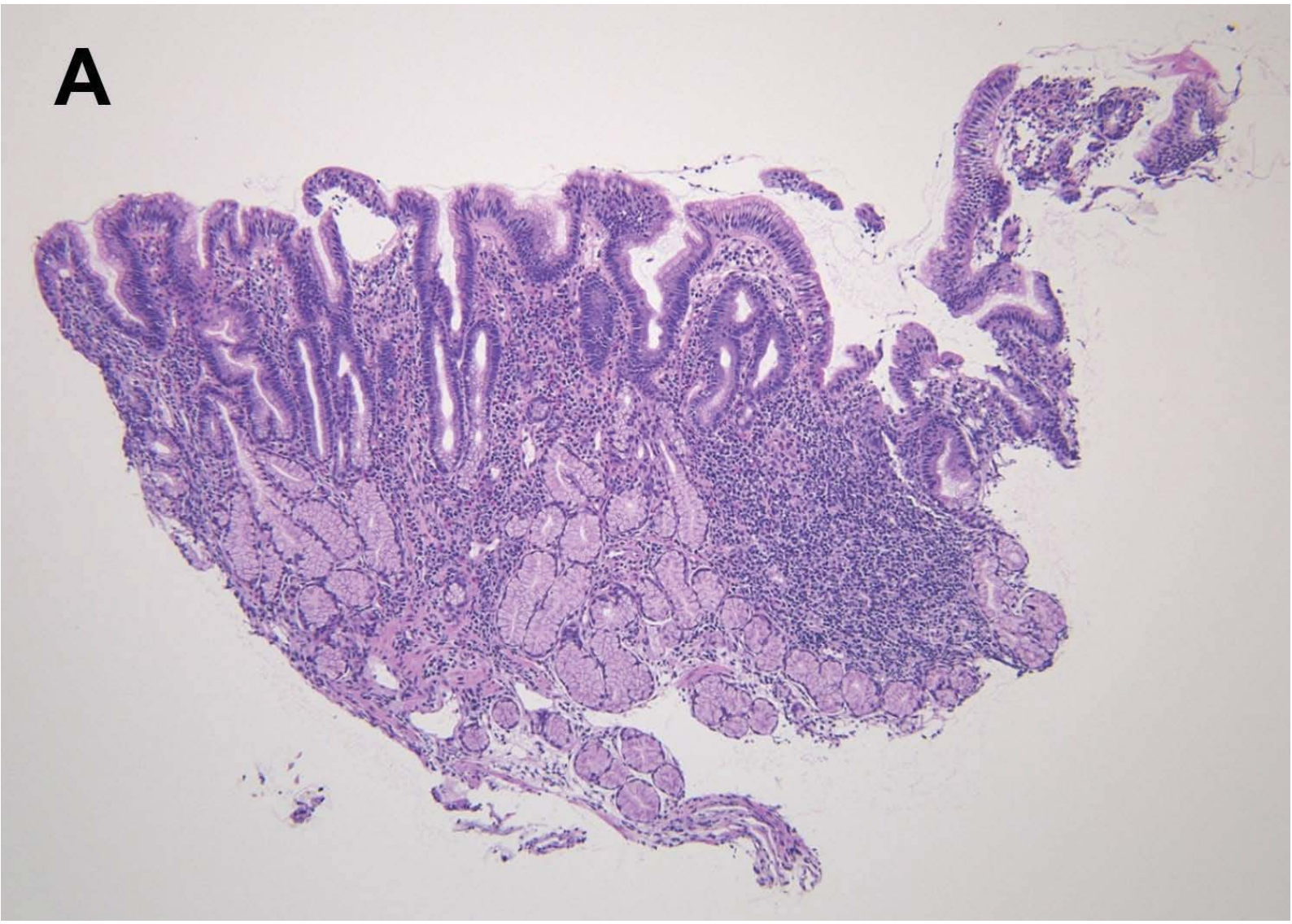
CD = Crohn's disease, BD = Behçet's disease, VA = villous atrophy, GM = gastric metaplasia, NA = notch-like appearance

TABLE 8. The correlation of PPI usage and frequency of duodenal gastric foveolar metaplasia

		duodenal gastric foveolar metaplasia		
		positive	negative	total
PPI	users	9	21	30
	not users	24	29	53
total		33	50	83

PPI = Proton pomp inhibitor

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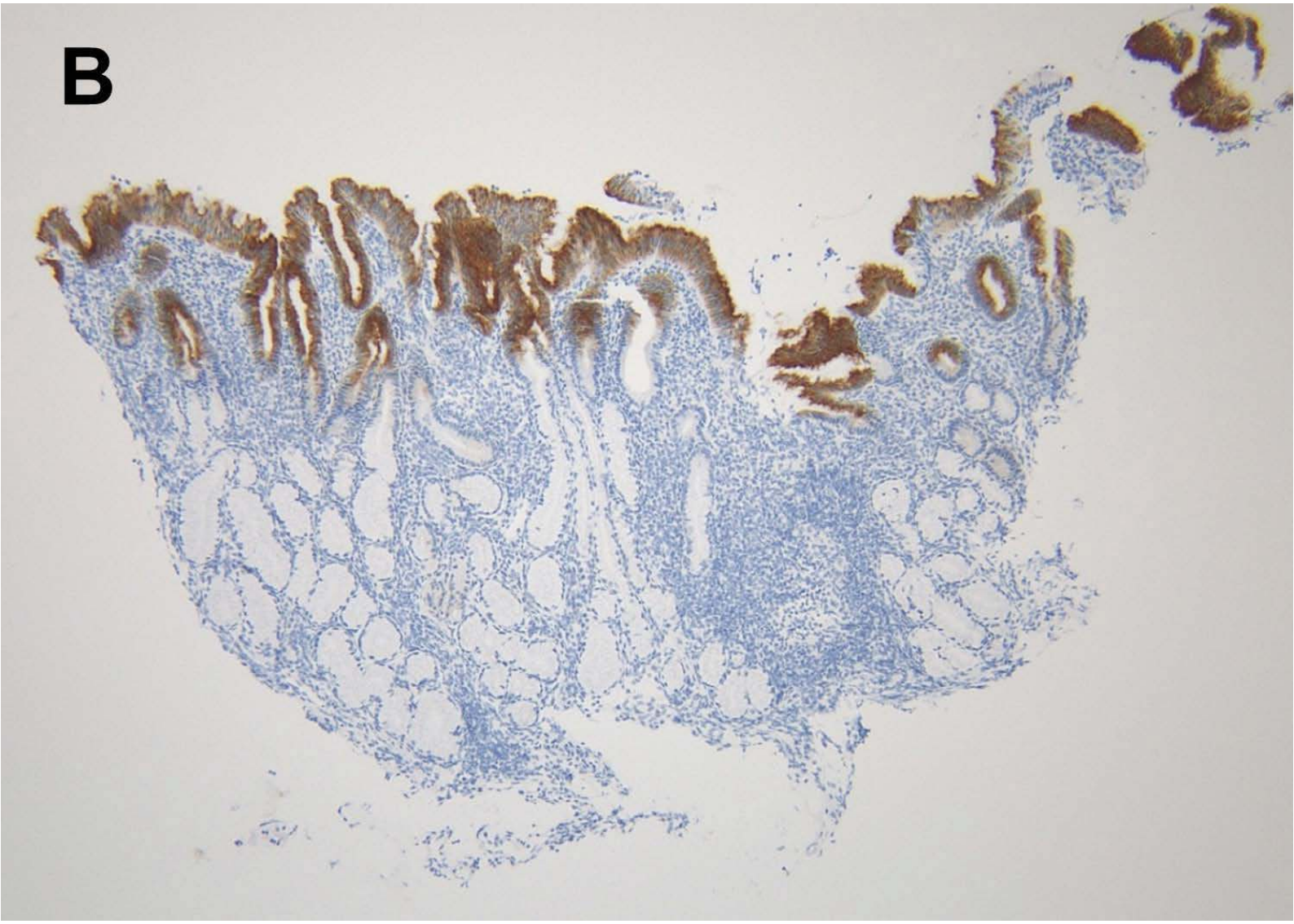
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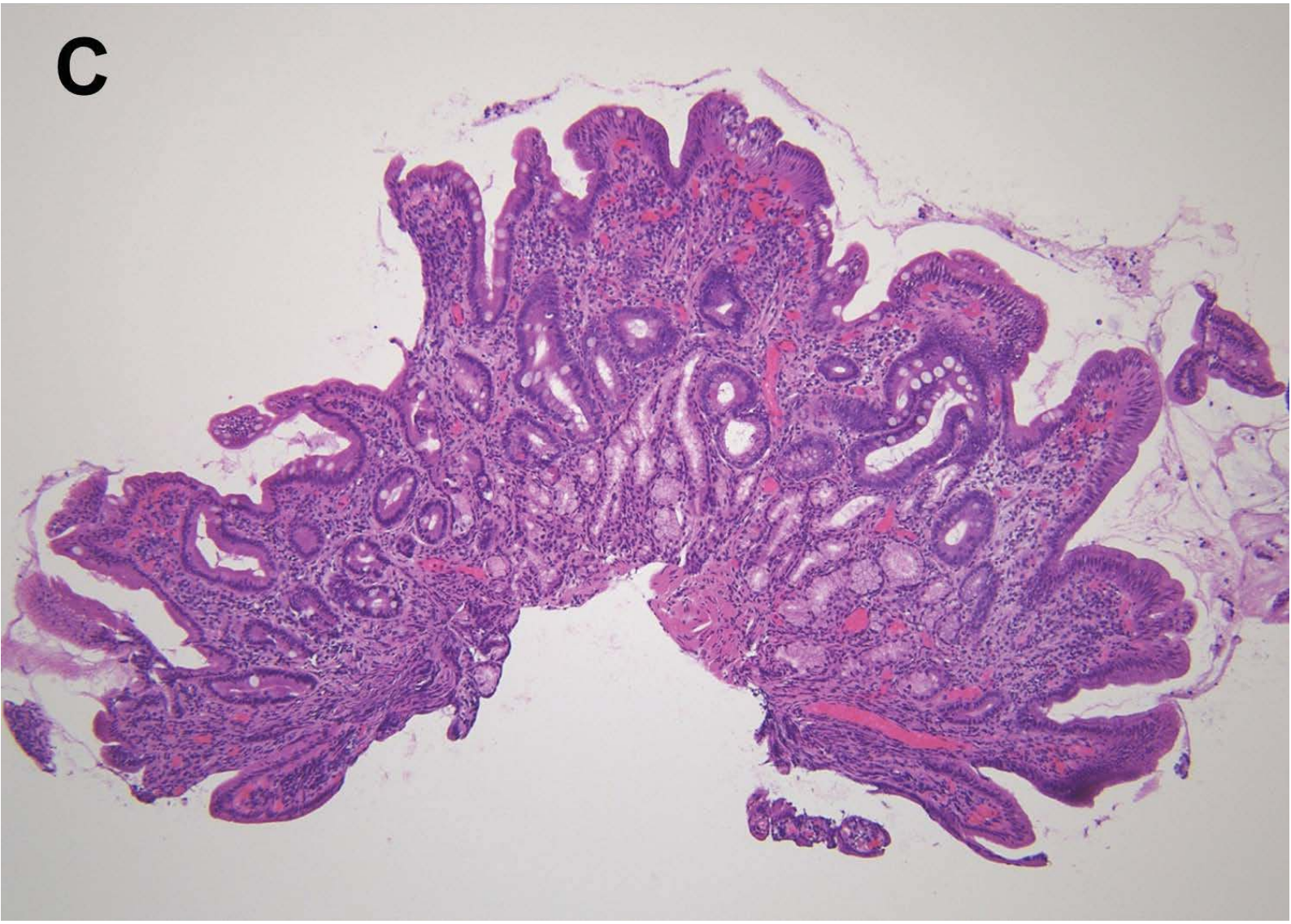
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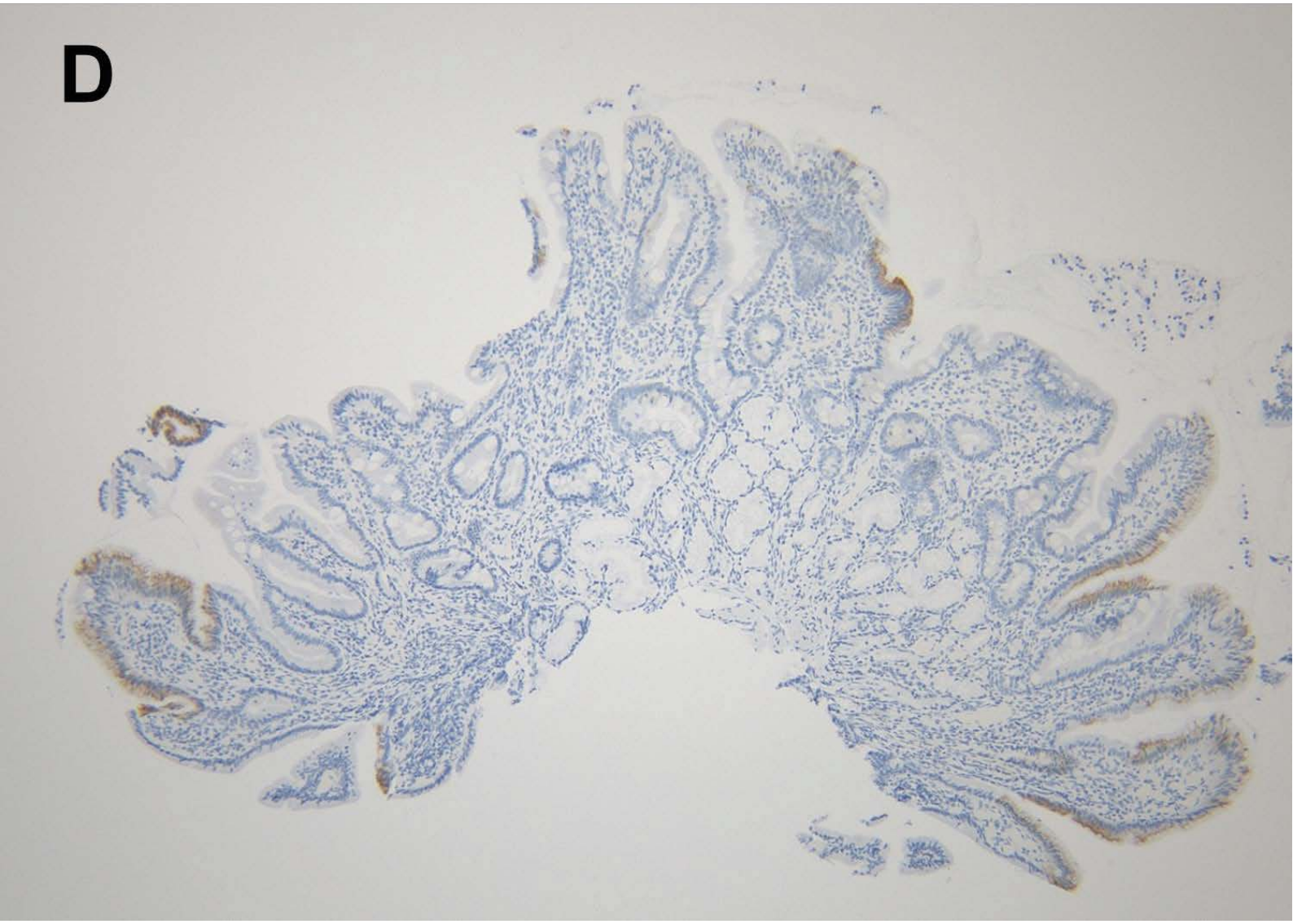
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