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【 CASE REPORT 】

Eosinophilic Gastroenteritis-associated Duodenal Ulcer Successfully Treated with Crushed Budesonide

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Abstract:
Eosinophilic gastroenteritis (EGE)-associated duodenal ulcer is rare and its endoscopic and pathological features remain poorly described. A 15-year-old boy was referred to our hospital for further examination and treatment of duodenal ulcer. Esophagogastroduodenoscopy (EGD) revealed two A2-stage duodenal ulcers on the duodenal bulb. A biopsy revealed marked infiltration of eosinophils, suggestive of EGE-associated duodenal ulcers. Thus, treatment with crushed budesonide (9 mg/day) was started. EGD revealed healing of the duodenal ulcers seven months after treatment. To our knowledge, this is the first report describing EGE-associated duodenal ulcer successfully treated with crushed budesonide.

Key words: eosinophilic gastroenteritis, duodenal ulcer, budesonide

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Introduction

Eosinophilic gastrointestinal diseases (EGIDs) are characterized by eosinophilic infiltration into the gastrointestinal tract, resulting in its morphological and functional abnormalities (1). EGIDs are classified into eosinophilic esophagitis (EoE) and eosinophilic gastroenteritis (EGE) according to the site of inflammation (2). EGE-associated duodenal ulcer is rare, and its endoscopic and pathological features remain poorly described.

We herein report a case of EGE-associated duodenal ulcer that was successfully treated with crushed budesonide.

Case Report

A 15-year-old boy visited a nearby clinic complaining of epigastric pain and nausea, which had appeared three weeks previously, as well as weight loss (3 kg). He was found to have mild anemia (Hb, 11.3 g/dL). Esophagogastroduodenoscopy (EGD) revealed two A2-stage duodenal ulcers on the anterior wall and greater curvature of the duodenal bulb (Fig. 1). While his epigastric pain had improved with 5 days of treatment with a potassium-competitive acid blocker (P-CAB), he developed a drug eruption and was switched to treatment with esomeprazole, a proton pump inhibitor (PPI). One month later, the patient was referred to our hospital for further examination and treatment.

Of note, he had a history of allergic rhinitis but no previous history of food allergy. Physical examination findings included: Height, 172.6 cm; weight, 70.6 kg; clear consciousness; blood pressure, 112/67 mmHg; heart rate, 81/min; and body temperature, 36.8°C. Laboratory findings showed mild anemia and slight elevation of the eosinophil count, nonspecific IgE, and gastrin. Specific IgE was false-positive for garlic but negative for other allergens. Serum *Helicobacter pylori* IgG antibody, stool *H. pylori* antigen, and rapid urease tests were all negative, suggesting that the patient was negative for *H. pylori* infection. Cytomegalovirus antigen and C7-HRP were also negative (Table 1). Ultrasonography (US) and computed tomography (CT) revealed thickening of the duodenal wall (Fig. 2A, B) but no ascites. One month after the initial endoscopic examination, a second endoscopic examination revealed A2-stage duodenal ulcers but no tendency toward healing of the ulcers, despite PPI treatment. A biopsy of the duodenal ulcers revealed

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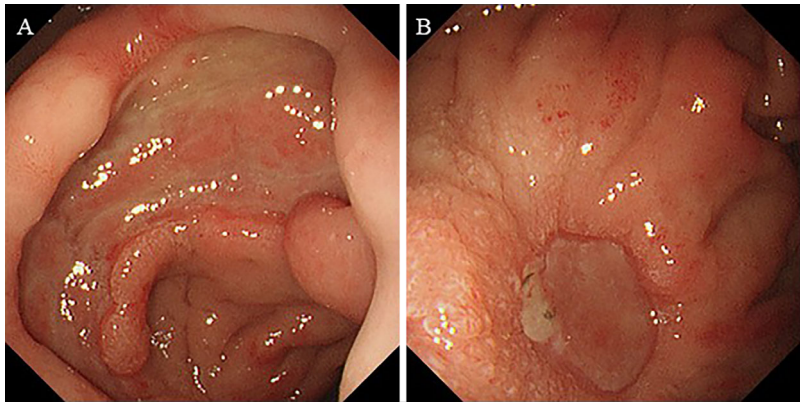

Figure 1. **Esophagogastroduodenoscopy (Initial). Two A2-stage duodenal ulcers were recognized on the anterior wall and greater curvature of the duodenal bulb (A, B).**

Table 1. **Laboratory Findings.**

WBC	5,000 /μL	Fe	7 μg/dL
Neut	53.5 %	ANA	<40 Index
Lymph	31 %	c-ANCA	<1.0 U/mL
Mono	5.8 %	p-ANCA	<1.0 U/mL
Eosino	9.1 %	CMV-IgM	Negative
Baso	0.6 %	CMV-IgG	Negative
RBC	4.76×10^6 /μL	CMV C7-HRP	Negative
Hb	11.7 g/dL	Serum *H. pylori* IgG antibody	<3 U/mL
Ht	38 %	Stool *H. pylori* antigen	Negative
Plt	303×10^3 /μL	Rapid urease test	Negative
TP	6.5 g/dL	Gastrin	215 pg/mL
Alb	4.5 g/dL	Nonspecific IgE	284 IU/mL
LDH	160 IU/L	Specific IgE	
AST	16 IU/L	Garlic	0.35 UA/mL
ALT	12 IU/L		
ALP	448 IU/L		
γ-GTP	14 IU/L		
T-Bil	0.76 mg/dL		
Na	142 mEq/L		
K	4.1 mEq/L		
Cl	105 mEq/L		

Alb: albumin, ALP: alkaline phosphatase, ALT: alanine aminotransferase, ANA: anti-nuclear antibody, AST: aspartate aminotransferase, Baso: basophils, CMV: cytomegalovirus, c-ANCA: c-anti-neutrophil cytoplasmic antibody, Cl: chloride, CMV C7-HRP: cytomegalovirus antibody-C7-HRP, CMV-IgG: cytomegalovirus antibody-immunoglobulin G, CMV-IgM: cytomegalovirus antibody-immunoglobulin M, Eosino: eosinophils, Fe: iron, g-GTP: g-glutamyl transpeptidase, *H. pylori*: *Helicobacter pylori*, IgE: immunoglobulin E, K: potassium, LDH: lactate dehydrogenase, Lymph: lymphocytes, Mono: monocytes, Na: sodium, Neut: neutrophils, Plt: platelets, RBC: red blood cell count, T-Bil: total bilirubin, TP: total proteins, WBC: white blood cell count

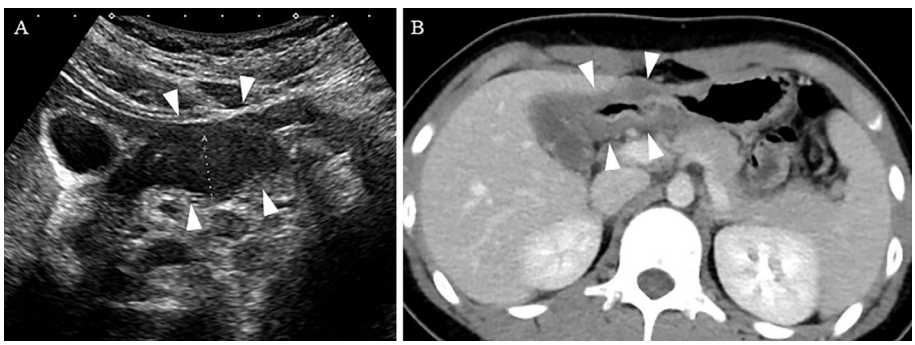

Figure 2. **Ultrasonography (US) and computed tomography (CT). US and CT revealed thickening of the duodenal wall, but no ascites (A, B).**

marked infiltration of eosinophils [20/high-pass filter (HPF)] (Fig. 3). Endoscopic findings on the esophagus (Fig. 4A), stomach (Fig. 4B-D), ileum (Fig. 4E), and colon (Fig. 4F-I) were normal, but biopsies from the gastric antrum, ileum, cecum, and ascending colon revealed marked eosinophilic infiltration (≥ 20/HPF) (Fig. 5B, E-G). Biopsies from the esophagus, the greater curvature of the gastric body, and the lesser curvature of the gastric angle showed no eosinophilic infiltration (Fig. 5A, C, D). In contrast, biopsies from the sigmoid colon and the rectum showed chronic inflammatory cell infiltration, but very few eosinophils (Fig. 5H, I).

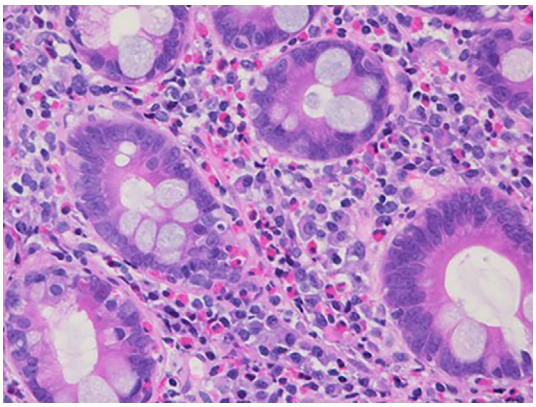

Figure 3. Histopathologic examination. A biopsy of the duodenal ulcer revealed marked eosinophilic infiltration (≥20/HPF). HPF: high-pass filter

The patient was diagnosed with EGE-associated duodenal ulcer based on the relevant diagnostic criteria and was given treatment with crushed budesonide 9 mg/day in addition to esomeprazole. The off-label use of budesonide was approved by our hospital's ethics committee and written informed consent was obtained from the patient and his family. At two weeks after the initiation of treatment, a third endoscopic examination revealed an improvement in the stage of the duodenal ulcers to H1 and S2 (Fig. 6). At seven months after treatment, a fourth endoscopic examination revealed complete healing of the duodenal ulcers (Fig. 7). The patient had no symptoms for one year after treatment with budesonide and his anemia and weight loss improved.

Discussion

Our case offers two important clinical implications. First, EGE may present as a duodenal ulcer in patients without *H.*

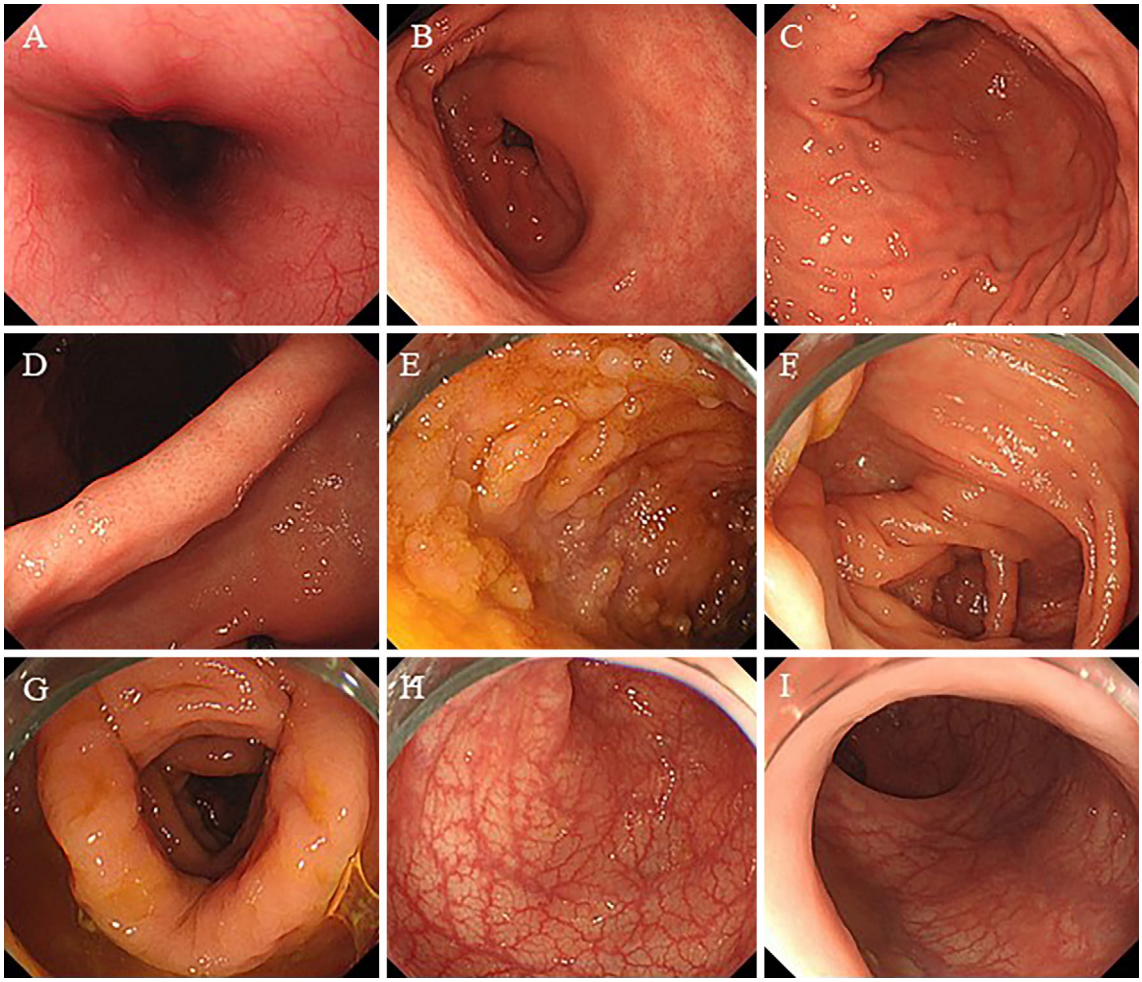

Figure 4. Esophagogastroduodenoscopy and colonoscopy (Initial). The endoscopic findings of the esophagus (A), stomach (B-D), ileum (E), and colon (F-I) were normal.

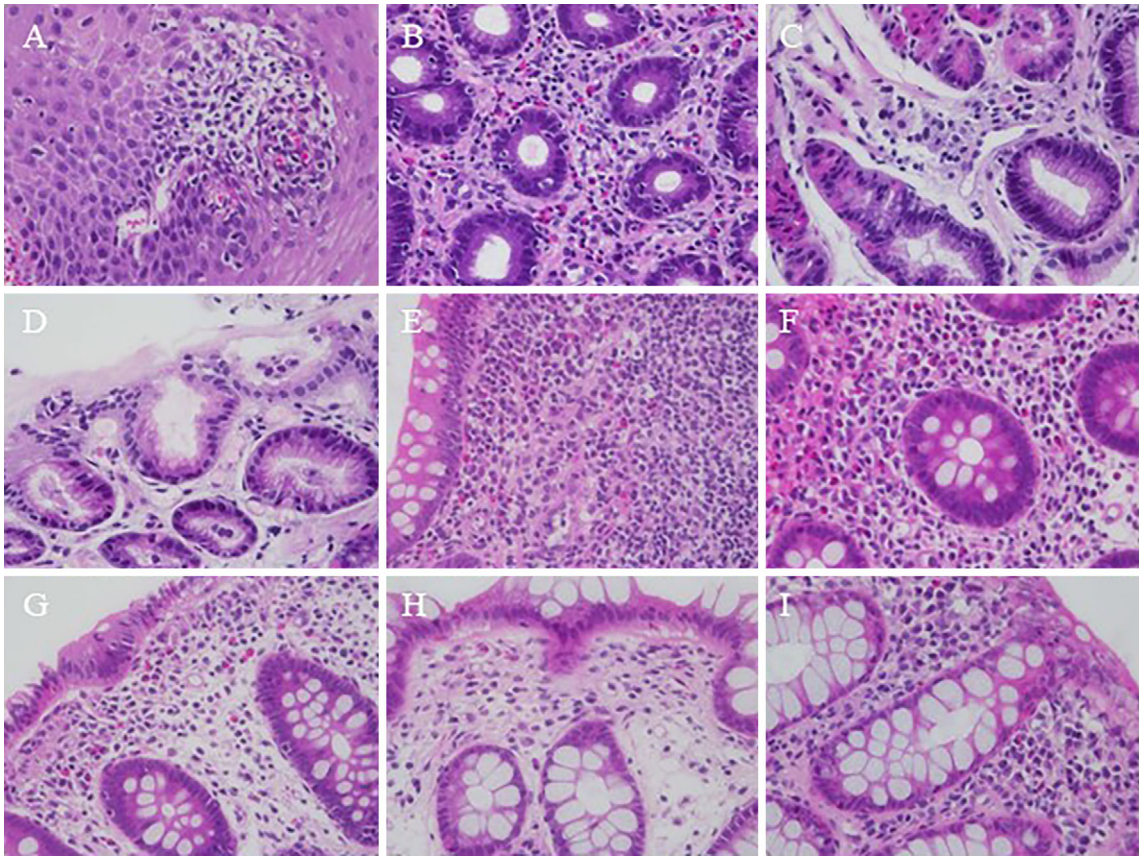

Figure 5. **Histopathologic examination. Biopsies from the gastric antrum (B), ileum (E), cecum (F), and ascending colon (G) revealed marked eosinophilic infiltration (≥20/HPF). Biopsies from the esophagus (A), the greater curvature of the gastric body (C), and the lesser curvature of the gastric angle (D) showed no infiltration of eosinophils. In contrast, biopsies from the sigmoid colon (H) and the rectum (I) showed chronic inflammatory cell infiltration but very few eosinophils. HPF: high-pass filter**

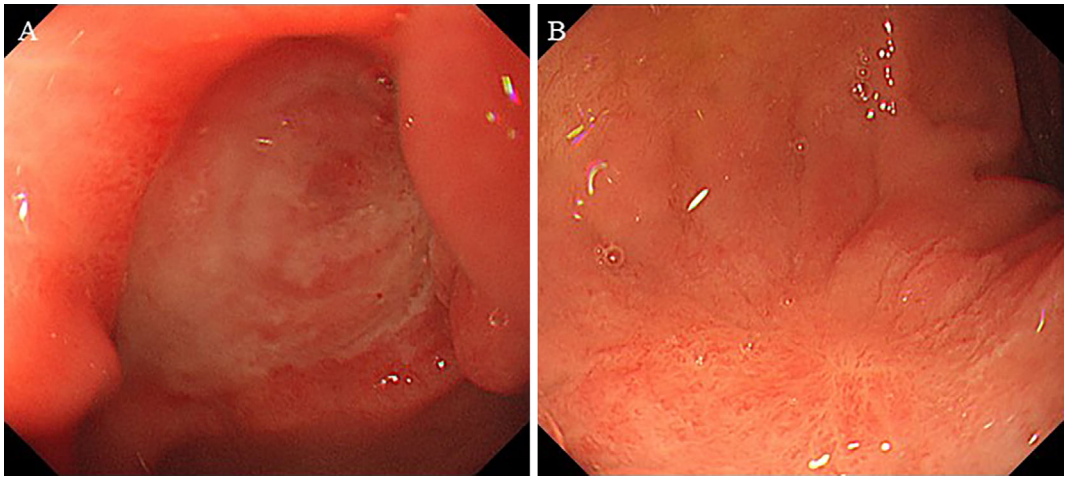

Figure 6. **Esophagogastroduodenoscopy (EGD) (2 weeks after treatment). EGD revealed improvement in the stages of the duodenal ulcers to H1 and S2 (A, B).**

pylori infection who are not treated with NSAIDs (non-*H. pylori,* non-NSAID ulcer), which is rare. Second, crushed budesonide was effective for promoting the healing of eosinophilic gastroenteritis-associated duodenal ulcers.

The following diagnostic criteria proposed by Talley are widely used for EGE: 1) presence of gastrointestinal (GI) symptoms, 2) histological demonstration of eosinophilic infiltration in the GI tract or the presence of a high eosinophil count in ascites, and 3) exclusion of other causes of tissue eosinophilia (3). Zhang et al. reported that while clinical symptoms, endoscopic findings, and radiologic findings are crucial in the diagnosis of EGE, pathological findings from

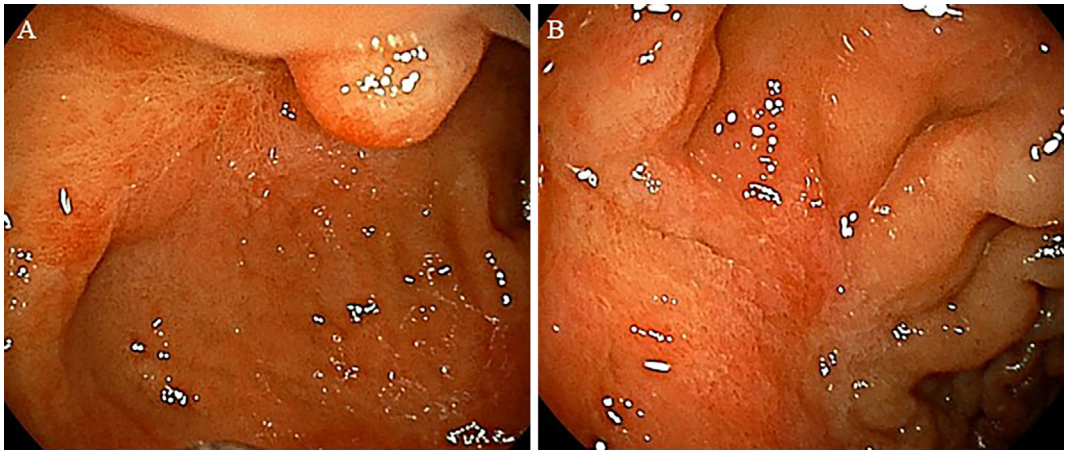

Figure 7. **Esophagogastroduodenoscopy (EGD) (7 months after treatment). EGD revealed healing of the duodenal ulcers (A, B).**

Table 2. **The Diagnostic Criteria for Eosinophilic Gastroenteritis in Japan (2012).**

1	Gastrointestinal (GI) symptoms
2	Infiltration of inflammatory cells mainly composed of eosinophils in the mucosa of the stomach, small intestine, and colon
3	Ascites and multiple eosinophils in ascites
4	History of allergic diseases
5	Eosinophilia in peripheral blood
6	Thickening of the GI tract wall by CT
7	Edema, redness, and erosion of the GI tract as confirmed by endoscopy
8	Effectiveness of glucocorticoid

1 and 2 or 1 and 3 designated as mandatory.

Table 3. **Cases Reported to Date of Eosinophilic Gastroenteritis-associated Duodenal Ulcer.**

No	Reference	Age	Sex	Perforation	Endoscopic findings	Treatment
1	[6]	11	M	(+)	Edematous and hyperemic duodenal bulb with a scar	PSL
2	[7]	11	F	(-)	Duodenal ulcer with surrounding edema and erythema	PSL (20 mg)
3	[8]	26	M	(+)	Duodenal ulcer with stenosis following laparotomy for perforated duodenal ulcer	PSL
4	[9]	27	M	(-)	Large ulcer with fold convergence	PSL (40 mg)
5	[10]	Early teens	M	(-)	Ulcer with a thickened, deep, white, moss-like appearance and marked edema at its edge	PSL (15 mg)
6	[11]	16	M	(+)	Residual duodenal ulcer after repair	Restrictive diet
7	[12]	54	M	(-)	Swollen and inflamed mucosal change with ulceration	PSL (30 mg) and montelukast (4 mg)
8	[13]	20	M	(-)	Extensive ulcer over half the circumference	PSL (40 mg)
9	Our case	15	M	(-)	Two A2-stage duodenal ulcers	Crushed budesonide (9 mg)

A2: active stage 2, F: female, M: male, PSL: prednisolone

multiple biopsies are the most important (4). Of the diagnostic criteria in Japan (Table 2) (5), the patient in the present case met criteria 1, 2, 4-6, 8 and was therefore diagnosed with EGE.

Endoscopic findings of EGE reported to date include edema, redness, erosion, and ulcer (1). Again, EGE-associated duodenal ulcer is rare, with only 8 cases reported in the relevant literature (6-13). The majority of these cases were reported in patients in their teens or twenties. Interestingly, three of these cases were diagnosed by EGD after the repair of the duodenal perforation (Table 3). Recently, Kanno et al. reported that the incidence of non-*H. pylori,*

non-NSAID ulcer in a multicenter prospective study conducted in Japan was 12% (46/382) (14). Thus, given the decreasing incidence of *H. pylori* infection in Japan, which is expected to increase the proportion of non-*H. pylori,* non-NSAID ulcer cases, EGE should receive more attention as a potential cause of non-*H. pylori,* non-NSAID ulcer.

The second implication of our case is that EGE-associated duodenal ulcer was successfully treated with crushed budesonide. Budesonide is a glucocorticoid-filled capsule that exerts highly potent, localized anti-inflammatory activity. The enteric-coated budesonide capsule was designed to release the drug in the distal small intestine, with 59-68% of the released drug being absorbed by the ileum and cecum. The systemic bioavailability following the oral administration of budesonide was approximately 11% (15). In addition, budesonide undergoes extensive first metabolism (80-90%) via the cytochrome P450-3A4 (CYP3A4) pathway to form two major metabolites: 6β-hydroxybudesonide and 16 α-hydroxy-prednisolone (16). These metabolites have no anti-inflammatory action and are mainly excreted in the urine and stool. Therefore, budesonide has fewer side effects, such as moon face, osteoporosis, and fracture, than prednisolone. In Japan, budesonide was approved in 2016 for remission induction in patients with mild-to-moderate active Crohn's disease. Again, budesonide has been shown to be effective for the treatment of EGE (17-19). While budesonide may be crushed, opened, or swallowed intact for use, the use of crushed budesonide allows the time- and PH-dependent release of the drug into the stomach (19). Therefore, crushed budesonide was used with very few side effects in our patient with EGE-associated duodenal ulcers due to unknown allergens, instead of prednisolone (PSL) or dietary restriction, which have been reported in the relevant literature (Table 3). To the best of our knowledge, this is the first report describing a case of EGE-associated duodenal ulcer successfully treated with crushed budesonide.

In conclusion, EGE may present as duodenal ulcer. It appears to be crucial to perform a biopsy for suspected EGE for patients with intractable duodenal ulcer. In addition, crushed budesonide may be an effective treatment for EGE-associated duodenal ulcer.

The authors state that they have no Conflict of Interest (COI).

KK, NK, KM, SM, MT, and MK contributed equally to this work.

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