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【 ORIGINAL ARTICLE 】

# Prevalence and Distribution of Gastric Endoscopy Findings in Non-eosinophilic Esophagitis Eosinophilic Gastrointestinal Diseases: Influence of Atrophic Gastritis

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**Abstract:**

**Objective** The impact of *Helicobacter pylori* infection on gastric endoscopic findings in non-eosinophilic esophagitis eosinophilic gastrointestinal diseases (non-EoE EGIDs) remains unclear. This study investigated the influence of *H. pylori* infection on the prevalence and distribution of gastric lesions.

**Methods** The details of 75 patients diagnosed with non-EoE EGIDs were retrospectively reviewed. Of the 56 patients with a definitive diagnosis according to the Japanese criteria (any GI tract; ≥20 eosinophils/high-power field), 25 patients with pathologic gastric eosinophilic infiltration (EI) (gastric EI; ≥30 eosinophils/high power field) were investigated in detail. The prevalence and distribution of gastric endoscopy findings were assessed according to the gastric mucosal atrophy status, an indicator of *H. pylori* infection.

**Results** Erythema (76%) was the most common finding in the gastric EI-positive group, followed by erosions (36%), ulcers (28%), ulcer scars (28%), and edema (24%). None of these lesions differed significantly in frequency between the patients with and without gastric atrophy. When erosions, ulcers, and ulcer scars were unified, they were slightly more common in the gastric bodies of patients with gastric atrophy than those without gastric atrophy; however, no preferential site was found in those without gastric atrophy. We identified six patients with active gastric ulcers, and half had large, deep ulcers with marginal swelling/irregularity.

**Conclusion** Gastric endoscopy findings in non-EoE EGIDs with gastric EI were evenly observed in the stomach, with no specific trend in frequency or distribution depending on atrophic gastritis, an indicator of *H. pylori* infection. Gastric ulcers in patients with non-EoE EGIDs should be considered in the differential diagnosis of idiopathic peptic ulcers.

**Key words:** non-EoE EGIDs, eosinophilic gastritis, gastric endoscopy findings, atrophic gastritis, *H. pylori* infection

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## Introduction

Eosinophilic gastrointestinal diseases (EGIDs) are chronic and refractory inflammatory conditions that are T helper 2 (Th2) cell-mediated and are characterized by intense eosinophilic infiltration (EI) and consequent dysfunction of the gastrointestinal (GI) tract. EGIDs are conventionally classified as eosinophilic esophagitis (EoE), in which eosinophilic inflammation is limited to the esophagus, or eosinophilic gastroenteritis (EGE), in which the gastrointestinal tract is broadly affected, irrespective of esophageal involvement (1). A new term, "non-EoE EGIDs," has been proposed for EGE, which is now subclassified into eosinophilic gastritis (EoG), eosinophilic enteritis (EoN), and eosinophilic colitis (EoC) according to the affected GI site (2).

Histological documentation of pathological EI in the GI tract is essential for the definitive diagnosis of EGIDs (1). Some characteristic endoscopic findings, such as edema, rings, white exudates, furrows, and strictures, are associated with EoE and influence endoscopists' decision to perform esophageal biopsies (3, 4). In contrast, endoscopic findings in non-EoE EGIDs are nonspecific throughout the GI tract (5-9). While most patients with EoE have at least one endoscopic abnormality (10, 11), 40-80% of patients with non-EoE EGIDs have been reported to have no abnormal findings on endoscopy (7, 8, 11). In addition, non-EoE EGIDs are rare, making endoscopists unlikely to suspect their occurrence or obtain biopsies (12).

*Helicobacter pylori* infection is closely associated with various diseases, such as chronic gastritis, peptic ulcers, mucosa-associated lymphoid tissue lymphoma, and gastric cancer (13). *H. pylori* and its induced gastritis can influence the severity and topography of gastric ulcers (14-17), portal hypertensive gastropathy (18, 19), and gastric fundic gland polyps or adenomas in familial adenomatous polyposis (20). However, the impact of *H. pylori* infection on gastric endoscopic findings in non-EoE EGIDs remains unclear.

Identifying and characterizing common endoscopic findings in non-EoE EGIDs will increase clinical awareness and inform gastroenterologists of subsequent definitive procedures. We therefore investigated whether or not *H. pylori* infection influences the prevalence and distribution of gastric endoscopic findings in patients with non-EoE EGIDs.

## Materials and Methods

This multicenter retrospective survey included 10 institutions. First, we collected the clinical information, endoscopy findings, images, and biopsy results of patients diagnosed with non-EoE EGIDs at each institution. Details such as the age, sex, body mass index, alcohol consumption, comorbid allergic diseases, GI symptoms, duration of non-EoE EGIDs, results of blood tests, serum anti-*H. pylori* antibodies, history of *H. pylori* eradication, number of gastric biopsies, gastric eosinophil count, other GI tract eosinophil counts, and medications were obtained. Gastric endoscopy images were also collected at the first diagnosis or at the point of highest disease activity for each patient from each institution.

Fig. 1 illustrates the patient selection process used in this study. A total of 75 enrolled patients were carefully reexamined based on the practical guidelines proposed by the EGID research group of the Ministry of Health, Labour and Welfare in Japan (21). For the definitive diagnosis of non-EoE EGIDs, guidelines require pathologic eosinophilia in the GI tract, defined as ≥20 eosinophils per high-power field (eos/HPF) (21). Consequently, 11 patients were excluded because of secondary GI tract eosinophilia (n=6), failure to meet the diagnostic criteria (n=2), duplicate registration (n=2), or a lack of endoscopic images (n=1). Seven patients were excluded from any group because they either did not undergo gastric biopsies or had unknown peak counts of infiltrating eosinophils. To more strictly define pathologic gastric EI in this study, we used a histologic criterion of ≥30 eos/HPF in gastric biopsies (22). Finally, the 56 patients were divided into 2 groups: the gastric EI-positive group (≥30 eos/HPF, n=25) and the gastric EI-negative group (<30 eos/HPF, n=31) (Fig. 1).

We compared the prevalence and distribution of gastric endoscopic findings in the gastric EI-positive group according to the presence or absence of gastric mucosal atrophy, an indicator of *H. pylori* infection. Endoscopic lesions such as erythema, erosions, ulcers, ulcer scars, granular/cracked mucosa, and discoloration were identified with reference to a recent report by Fujiwara et al. (23). Figs. 2-4 show representative images of our cases. These lesions were also captured according to their specific location in the stomach (antrum, body, and both antrum and body). The gastric angle was included in the body. Mucosal defects <5 mm in diameter and those ≥5 mm in diameter were described as erosions and ulcers, respectively. Gastric mucosal atrophy was endoscopically assessed using the Kimura-Takemoto classification system. Mucosal atrophy was defined as positive if the lesion was classified as ≥C-2 and negative if it was classified as ≤C-1 (24).

All endoscopy images, including those for assessing gastric atrophy, were reviewed by three endoscopists board-certified by the Japanese Gastroenterological Endoscopy Society (N.M., Y.A., and Y.S.). When a discrepancy occurred, a final decision was made by consensus among the three endoscopists. This study was approved by the ethics committee of Yamagata University (approval no. 2021-57) and the ethics committee of each participating institution and was conducted in accordance with the Declaration of Helsinki.

### Statistical analyses

Data are presented as medians with interquartile ranges (IQR) or as numbers with percentages. For comparisons between two independent groups, continuous variables were analyzed using Wilcoxon's rank-sum test, and categorical variables were analyzed using the chi-square test or Fisher's

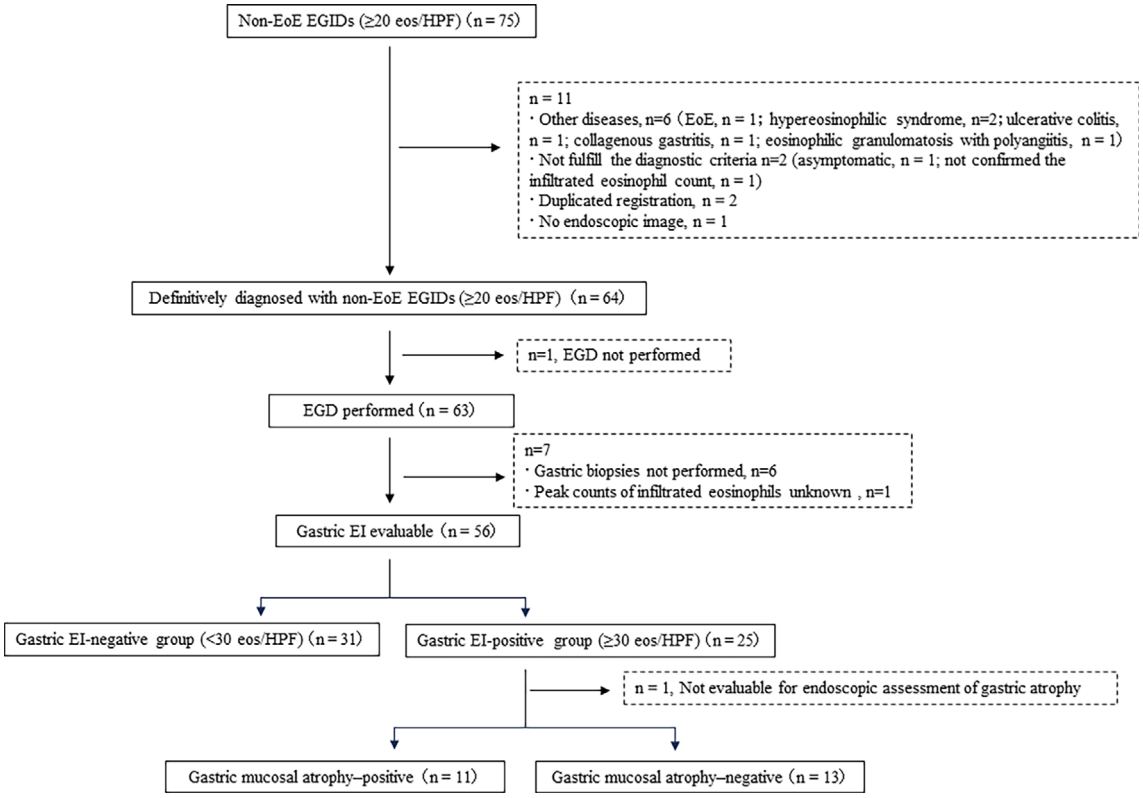


**Figure 1. Flowchart showing patients eligible for this study. Non-EoE EGIDs: non-eosinophilic esophagitis eosinophilic gastrointestinal diseases, EGD: esophagogastroduodenoscopy, EI: eosinophilic infiltration**

exact probability test. All statistical analyses were performed using the JMP® software program, version 14.1.0 (SAS Institute, Cary, USA). Statistical significance was set at $p< 0.05$.

## Results

### Clinical profiles of the patients investigated

Table 1 shows the basic clinical profiles of the 56 patients with non-EoE EGIDs, consisting of 31 gastric EI-negative and 25 gastric EI-positive patients.

The age at the first diagnosis was significantly older in the gastric EI-positive group than in the gastric EI-negative group (median, 55 vs. 46 years old, p=0.03). No significant differences between the two groups were found in the men-to-women ratio, body mass index, alcohol consumption, time from symptom onset to the diagnosis, presence of allergic conditions, GI symptoms, ascites, or blood test results. Serum *H. pylori* antibody results were available for fewer than half of the patients in both groups, most of whom tested negative for *H. pylori*. The history of *H. pylori* eradication in many patients is unknown. The number of gastric biopsies (median, 3 vs. 2; p=0.02) and gastric eosinophil count (median, 71 vs. 12 eos/HPF; p<0.0001) were significantly higher in the gastric EI-positive group than in the gastric EI-negative group.

Eosinophil infiltration at other GI sites in gastric EI-positive and EI-negative patients is shown in Supplementary material 1. Eleven (35%) of the 31 gastric EI-negative patients had gastric EI of ≥20 eos/HPF but <30 eos/HPF. Of the remaining 20 patients with gastric EI of <20 eos/HPF, 14 (70%), 7 (35%), and 13 (65%) had eosinophil infiltration of ≥20 eos/HPF in the duodenum, ileum, and colon, respectively. The gastric EI-positive group received proton pump inhibitor therapy significantly more commonly than the gastric EI-negative group (Supplementary material 2). The administration of other medications, such as systemic corticosteroids, topical corticosteroids, and anti-allergic agents, was not markedly different between the two groups. There were no users of non-steroidal anti-inflammatory drugs (NSAIDs) in either group.

### Gastric endoscopy findings

Table 2 shows the prevalence of gastric endoscopy findings and compares them between the gastric EI-positive and EI-negative groups. Erythema (76%) was the most common finding in the gastric EI-positive group, followed by erosions (36%), ulcers (28%), ulcer scars (28%), and edema (24%). Erosions, ulcers, and ulcer scars were more frequent in the gastric EI-positive group than in the gastric EI-negative group, but the difference was not statistically significant. When these 3 findings were combined, a statistically significant difference was observed between the 2 groups (p=0.04). One patient with gastric ulcer in the gastric EI-positive group, who was not endoscopically evaluable for

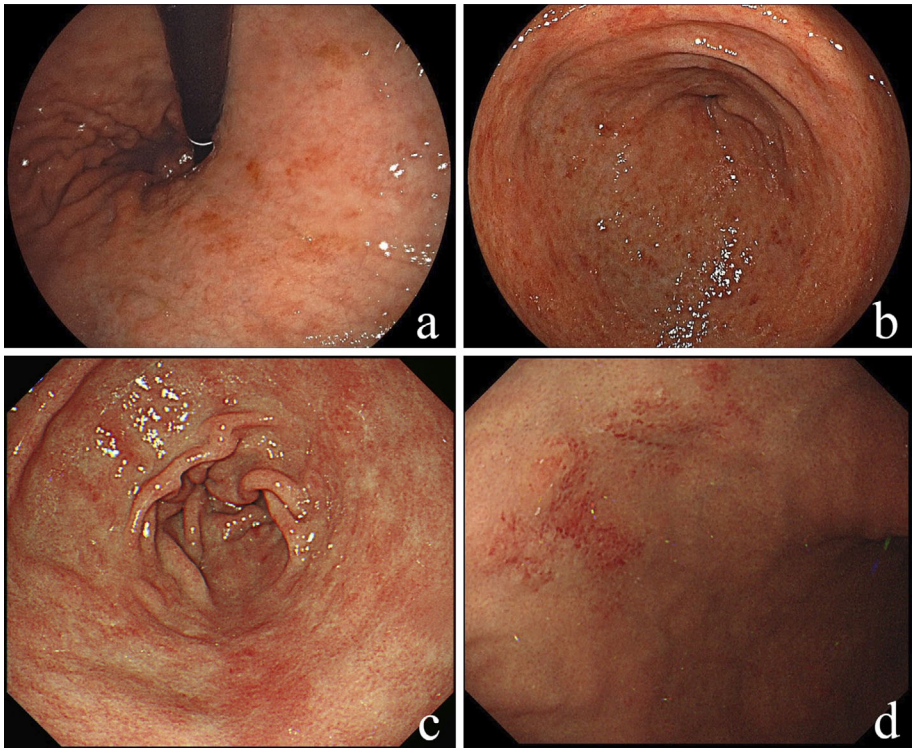


**Figure 2. Representative images of erythema on endoscopy. Spot lesions or patchy red areas were visible. (a) Patchy redness in the lesser curvature of the gastric body; (b, c) spot lesions or patchy red areas in the antrum; (d) patchy redness in the anterior wall of the gastric body.**

gastric atrophy, was excluded from the subsequent analysis.

Fig. 5 depicts the prevalence of gastric endoscopic findings in the EI-positive group (n=24) based on the presence or absence of gastric atrophy. There was also no significant difference between the two groups (positive vs. negative mucosal atrophy) in other endoscopic findings such as erosions, ulcers, ulcer scars, discoloration, edema, and granular/cracked mucosa. For ease of reporting, we combined erosions, ulcers, and ulcer scars as a single entity. Fig. 6 shows the prevalence of endoscopy findings according to the presence or absence of gastric atrophy and location of the lesion in the stomach. Erythema was less common in the antrum of patients without gastric mucosal atrophy than in those with atrophy; however, there was no significant difference between the two groups (Fig. 6a). Erosions, ulcers, and ulcer scars were observed in approximately half of the patients in both the groups (Fig. 6b). These lesions were commonly found in the gastric body of patients with atrophy, but the difference was not statistically significant. Patients without gastric mucosal atrophy displayed an even distribution of the lesions throughout the stomach.

### *Morphological features of active gastric ulcers*

In addition, we examined the morphological features of active gastric ulcers in six patients (four gastric atrophy-positive and two gastric atrophy-negative). Our findings and those of previously reported cases are summarized in Table 3. We reviewed six published studies describing the location and morphology of gastric ulcers in patients with non-EoE EGIDs. Generally, ulcers are multiple and vary in size and depth. Most ulcers larger than 2 cm in diameter have been reported to be deep and have an irregular outline with submucosal marginal swelling. In our study, large ulcers (>2 cm) occurred predominantly in the gastric body; however, no preferential location was observed when previous reports were considered. Five of the six patients had negative results for serum *H. pylori* antibody or post-eradication status. There were no cases of non-EoE EGIDs complicated by active bleeding.

## Discussion

In this study, we investigated the characteristics of gastric endoscopy findings in non-EoE EGIDs with pathologic eosinophilic infiltration in the stomach as well as their distribution and association with *H. pylori* infection. As previously reported (5-8, 23, 25), we noted various nonspecific endoscopic findings in the stomach, including erythema, erosion, ulcers, ulcer scars, discoloration, edema, and granular/cracked mucosa.

In our cohort, erythema was the most common finding (76%), followed by erosion (36%), ulcers (25%), and scars (28%). This is similar to the findings of two recent reports investigating gastric endoscopy findings in EoG (23, 26). A single-center retrospective study of 18 patients with EoG (defined as ≥20 eos/HPF) conducted in Japan showed that erythema was present in 72% of cases, erosions in 28%, and ulcers in 39% (23). Furthermore, a multicenter prospective

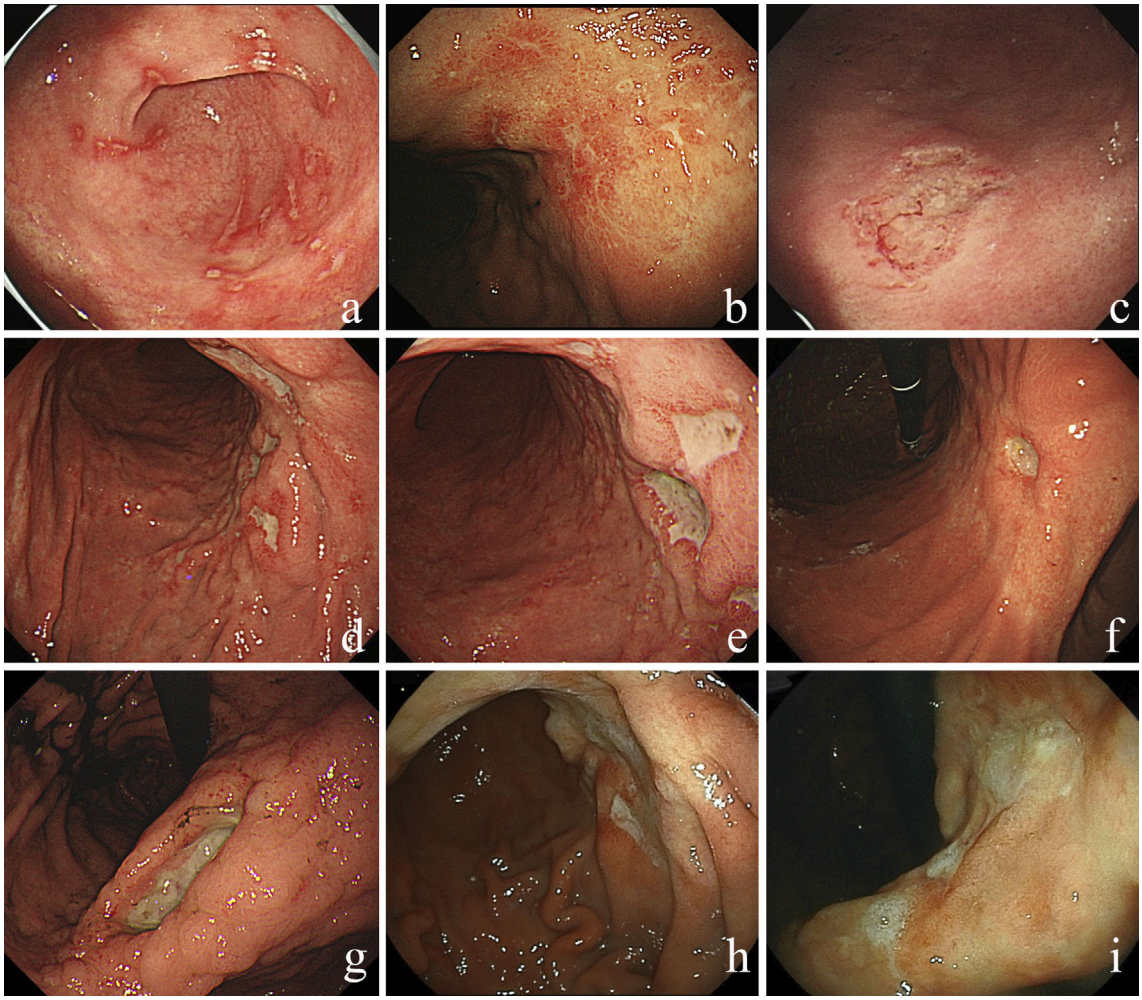


**Figure 3.** **Representative images of erosions and ulcers. (a, b) Multiple irregular erosions in the lower body; (c) shallow ulcer in the greater curvature of the gastric body; (d) multiple irregular and deep ulcers in the upper body; (e) close-up image of multiple ulcers shown in (d); (f) gastric ulcer with slightly swollen margins in the lower body; (g) deep ulcer in the angle; (h) multiple, shallow and irregular ulcers in the lower body; and (i) retrograde image of multiple ulcers shown in (h).**

study carried out in the United States demonstrated that erythema was present in 72% of 65 patients with EoG (defined as ≥30 eos/HPF), while erosions or ulcers were found in 46% of patients (26). In Japan, eosinophilic infiltration in the GI tract above 20 eos/HPF has been adopted for the diagnosis of non-EoE EGIDs in the practical guidelines proposed by the EGID research group of the Ministry of Health, Labour and Welfare (21). In the present study, however, we set a stricter cutoff value for gastric EI of ≥30 eos/HPF (22). Our results showed that mucosal injury findings, including erosions, ulcers, and ulcer scars, were significantly more common in the gastric EI-positive group than in the gastric EI-negative group, suggesting the appropriateness of the threshold for pathologic gastric EI (≥30 eos/HPF) used in this study. This could also be attributed to the significantly higher number of gastric biopsies in the gastric EI+ group.

Some reports have suggested that *H. pylori* infection or *H. pylori*-induced gastritis potentially modifies the endoscopic features of several conditions. An inverse relationship between the degree of vascular dilatation and *H. pylori* colonization in portal hypertensive gastropathy has been demonstrated, presumably because of mucosal hypoxia and vascular congestion (18). NSAIDs increase the risk of gastric ulcers in the lesser curvature, whereas *H. pylori* infection does so in the greater curvature (14). In addition, NSAIDs or low-dose aspirin induce mucosa injuries that are predisposed to occur in the antrum in the absence of *H. pylori* infection, with most shifting to the gastric body in the presence of concomitant *H. pylori* infection (15, 27-29). Iijima et al. reported that low-dose aspirin-induced gastropathy was predominant in the antrum of *H. pylori*-negative and *H. pylori*-positive gastric acid non-hyposecretors but was common in the body and fundus of *H. pylori*-positive gastric acid hyposecretors (16). Another study reported that *H. pylori* infection suppressed the development of fundic gland polyps in familial adenomatous polyposis but strongly promoted the development of gastric adenoma, especially in the presence of adenomatous polyposis coli mutations (20). However, no study has addressed the association between *H. pylori* infec-

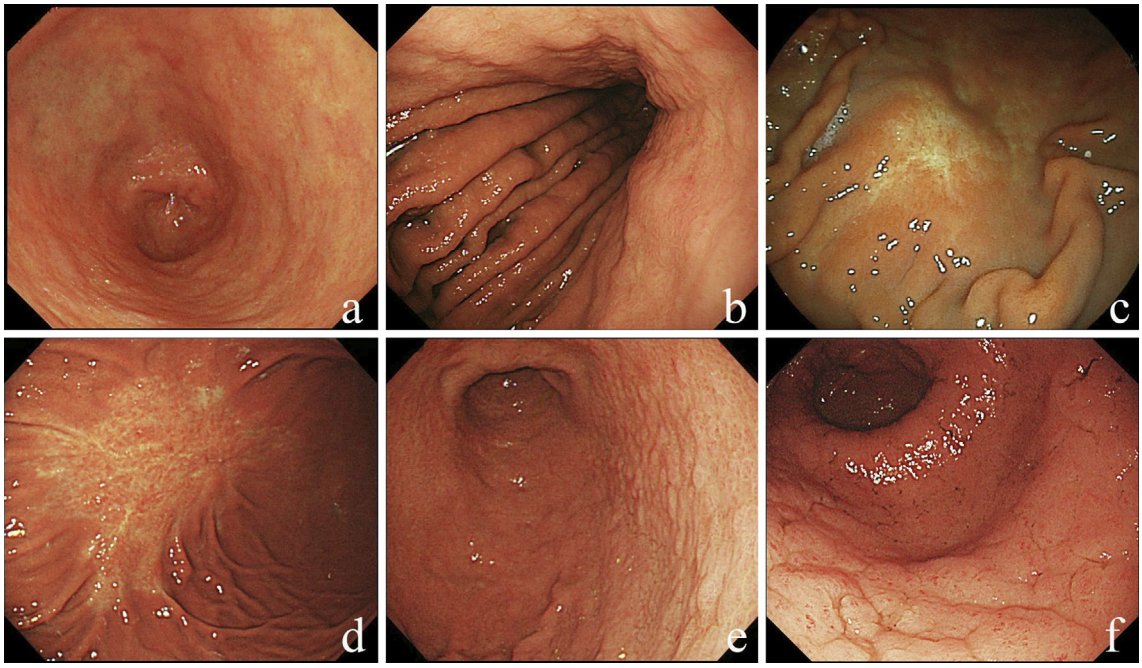


**Figure 4. Representative images of edema, discoloration, and granular/cracked mucosa. Edematous lesions in the (a) antrum and (b) body; (c, d) discoloration in the body; (e) granular mucosa in the lower body; and (f) cracked mucosa in the antrum.**

tion and the characteristics of gastric lesions in non-EoE-EGID patients.

Unfortunately, many of our patients were not fully assessed for *H. pylori* infection and eradication status; thus, we used the presence of mucosal atrophy on endoscopy as a surrogate indicator of infection (24). The prevalence of each endoscopy finding did not differ significantly between patients with and without gastric atrophy. In addition, the localization of erythema within the stomach was not significantly different between the two groups. For erosions, ulcers, and ulcer scars, there was a slight predilection for the gastric body in patients with gastric atrophy. However, no preferential site was found in those without gastric atrophy. This is consistent with two Japanese case series results that showed a comparable prevalence and degree of histological eosinophilic inflammation between the antrum and gastric body in non-EoE EGIDs (23, 25). In contrast, a recent multicenter cohort study from the United States revealed a substantially higher frequency and severity of gastric lesions in the antrum than in the body or fundus, with anatomical and functional differences or duodenal-gastric reflux hypothetically discussed as the underlying mechanisms (26). Racial differences, gastric acid secretory function, dietary habits, and environmental factors may also have contributed to this discrepancy.

Non-EoE EGID-related ulcers are an important consideration for the differential diagnosis of non-*H. pylori* and non-NSAID ulcers. A recent report showed that non-EoE EGID-related ulcers account for approximately 10% of non-*H. pylori* and non-NSAID ulcers in the Korean pediatric population (30). Peptic ulcers without secondary causes, such as non-EoE EGIDs, inflammatory bowel diseases, Zollinger-Ellison syndrome, or severe physical/psychological stress, are defined as idiopathic ulcers (IPUs), the proportion of which has been increasing (31). IPUs include gastric and duodenal ulcers, with the former accounting for 70-90% of cases (32-34). They have been reported to occur preferentially in the gastric antrum with swelling of the ulcer margin (17, 34-37) and are characterized by being refractory and easily recurrent (33, 38); in contrast, based on previous reports, including our present study, half of the active gastric ulcers in non-EoE EGIDs had large, deep, or multiple ulcers with swollen and irregular margins (Table 3, Fig. 3) (23, 39-43). Animal models of experimental ulcers or tissues from patients with perforated gastric ulcers have shown that eosinophils play a critical role in ulcer aggravation (44, 45). Indeed, two previous studies reported that intense transmural EI was demonstrated on the histological assessment of surgical samples obtained from patients with giant antral ulcers in non-EoE EGIDs (39, 40). Large and deep ulcers may indicate eosinophilic involvement of deeper layers of the gastrointestinal wall. In our study, such large and deep ulcers were more common in the body than in other areas; however, in other reports, they appeared to occur in both the antrum and gastric body. Owing to the wide heterogeneity of eosinophilic infiltration in the GI mucosa with or without organic lesions, biopsy specimens must be obtained from normal-appearing areas in addition to ulcer margins when non-EoE EGID-related ulcers are suspected (23, 46).

Several limitations associated with the present study warrant mention. Our small sample size and retrospective design

**Table 1. Basic Clinical Profile of Patients with Non-EoE EGIDs, Negative Gastric EI, and Positive Gastric EI.**

| | Non-EoE EGIDs (n=56) | Gastric EI-negative group (n=31) | Gastric EI-positive group (n=25) | p value |
|---|---|---|---|---|
| Male (%) | 31 (55.4) | 18 (58.1) | 13 (52) | 0.79 |
| Body mass index (mean) | 23.2 (20.1-26.1) | 23.9 (20-25.6) | 22 (20.2-26.4) | 0.94 |
| Alcohol drinking | | | | |
| Current | 13 (23.2) | 11 (35.5) | 2 (8) | |
| Previous | 2 (3.6) | 1 (3.2) | 1 (4) | 0.05[a] |
| None | 29 (51.8) | 13 (41.9) | 16 (64) | |
| Unknown | 12 (21.4) | 6 (19.4) | 6 (24) | - |
| Age at the first diagnosis, median (IQR) | 50.5(38-62.75) | 46 (28-57) | 55 (46-65.5) | 0.03 |
| Time from symptom onset to the diagnosis in months[b] | 1 (0.5-13) [n=53] | 1 (1-6.3) [n=30] | 1 (0-16) [n=23] | 0.73 |
| Allergic conditions (%) | | | | |
| Bronchial asthma | 16 (28.6) | 8 (25.8) | 8 (32) | 0.77 |
| Allergic rhinitis | 13 (23.2) | 10 (32.2) | 3 (12) | 0.11 |
| Atopic dermatitis | 5 (8.9) | 2 (6.5) | 3 (12) | 0.65 |
| Food allergy | 7 (12.5) | 4 (12.9) | 3 (12) | 1 |
| Drug allergy | 10 (17.9) | 6 (19.4) | 3 (12) | 0.72 |
| Any | 35 (62.5) | 22 (71.0) | 13 (52) | 0.17 |
| GI symptoms (%) | | | | |
| Dysphagia | 5 (8.9) | 1 (3.2) | 4 (16) | 0.16 |
| Abdominal pain | 47 (83.9) | 26 (83.9) | 21 (84) | 1 |
| Loss of appetite | 18 (32.1) | 10 (32.2) | 8 (32) | 1 |
| Nausea/vomiting | 21 (37.5) | 11 (35.5) | 10 (40) | 0.79 |
| Diarrhea | 22 (39.3) | 16 (51.6) | 6 (24) | 0.05 |
| Blood stool | 4 (7.1) | 1 (3.2) | 3 (12) | 0.31 |
| Others[c] | 16 (28.6) | 8 (25.8) | 8 (32) | 0.77 |
| Ascites (%) | 10 (17.9) | 7 (22.6) | 3 (12.5) [n=24] | 0.49 |
| Blood chemical test | | | | |
| White blood cells in cells/μL, median (IQR) | 7,350 (5,600-10,385) | 7,600 (5,300-13,500) | 6,700 (5,700-8,250) | 0.18 |
| Eosinophils in cells/μL, median (IQR) | 735 (219.3-2,438) | 1,190 (220-3,891) | 670 (209-1,272) | 0.14 |
| Serum albumin in g/dL, median (IQR) | 4.2 (3.9-4.4) | 4.3 (3.9-4.4) | 4.1 (3.9-4.6) | 0.55 |
| Serum *H. pylori* antibody | | | | |
| Positive | 2 (3.6) | 0 | 2 (8.0) | 0.49 |
| Negative | 19 (33.9) | 9 (29.0) | 10 (40.0) | |
| Unknown | 35 (62.5) | 22 (71.0) | 13 (52.0) | - |
| *H. pylori* eradication | | | | |
| Performed | 7 (12.5) | 4 (12.9) | 3 (12.0) | 0.59 |
| Not performed | 6 (10.7) | 2 (6.5) | 4 (16.0) | |
| Unknown | 43 (76.8) | 25 (80.6) | 18 (72.0) | - |
| Nunber of gastric biopsies, median (IQR) | 2 (2-3.75) | 2 (1-3) | 3 (2-4) | **0.02** |
| Gastric eosinophils count per HPF, median (IQR) | 25 (10-70) | 12 (1-22) | 71 (40-101) | **<0.0001** |

Non-EoE EGIDs: non-eosinophilic esophagitis eosinophilic gastrointestinal diseases, EI: eosinophilic infiltration, IQR: inter quartile range

[a]The current and previous group were combined and compared with the none group. The unknown group was not included.

[b]Time from symptom onset to the diagnosis and ascites were not aveilable in all patients. The notation in square brackets is the number of patients with available details.

[c]Other symotoms included one or more of heartburn, abdominal distention or dyspepsia.

might have led to an underestimation of the prevalence and distribution of endoscopy findings. Therefore, all endoscopy images were carefully reviewed by three board-certified endoscopists and were included based on consensus. Another critical limitation is our use of gastric mucosal atrophy on endoscopy for the indirect assessment of *H. pylori* infection, in addition to the absence of *H. pylori* eradication therapy. The status of *H. pylori* infection was more difficult to determine in this retrospective study than anticipated. However, we suppose that gastric mucosal atrophy could yield a sustained functional alteration irrespective of the eradication therapy and could be a reasonable indicator for assessing *H. pylori* infection (47). We used a cutoff of ≥30 eos/HPF for diagnosing pathologic gastric EI in this study; however, no international consensus concerning the most appropriate cut-off exists (22). We did not assess the extent of gastric EI based on each gastric endoscopy finding, which has been reported to not significantly differ in a previous report (23).

In conclusion, our present study showed that gastric endoscopy findings, such as erythema, erosions, or ulcers, in

**Table 2. Gastric Endoscopy Findings in the Gastric EI-positive and EI-negative Patients.**

| | Non-EoE EGIDs (n=56) | Gastric EI negative (n=31) | Gastric EI positive (n=25) | p value |
|---|---|---|---|---|
| Any abnormal findings | 46 (82.1%) | 23 (80.6%) | 23 (92%) | 0.16 |
| Erythema | 38 (67.9%) | 19 (61.3%) | 19 (76%) | 0.27 |
| Erosions/ulcers/ulcer scars[a] | 21 (37.5%) | 8 (25.8%) | 13 (52%) | **0.04** |
| Erosions | 14 (25%) | 5 (16.1%) | 9 (36%) | 0.12 |
| Ulcers | 9 (16.1%) | 2 (6.5%) | 7 (28%) | 0.06 |
| Ulcer scars | 9 (16.1%) | 2 (6.5%) | 7 (28%) | 0.06 |
| Discoloration | 5 (8.9%) | 2 (6.5%) | 3 (12%) | 0.65 |
| Edema | 14 (25%) | 8 (25.9%) | 6 (24%) | 1.00 |
| Granular/cracked mucosa | 6 (10.7%) | 3 (25.9%) | 3 (12%) | 1.00 |
| Others | 4 (7.1%) | 3 (9.7%) | 1 (4%) | 0.62 |

[a]Erosions and/or ulcers and/or ulcer scars.

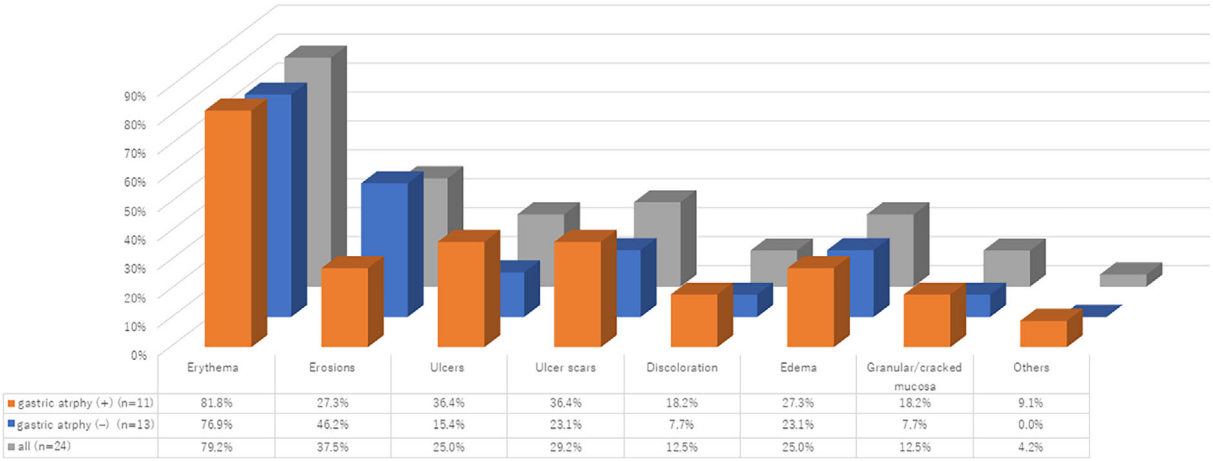


**Figure 5. Prevalence of gastric endoscopy findings in the gastric EI-positive group according to the gastric atrophy status. Gray column, all patients; orange column, patients with gastric atrophy; blue column, patients without gastric atrophy. EI: eosinophilic infiltration**

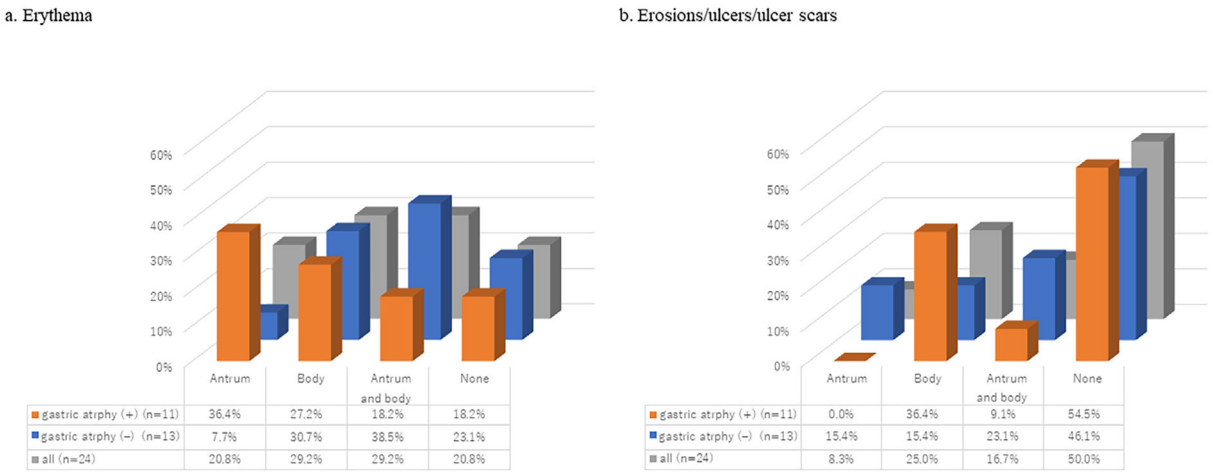


**Figure 6. Prevalence of (a) erythema and (b) erosions/ulcers/ulcer scars in the gastric EI-positive group according to the gastric atrophy status. Gray column, all patients; orange column, patients with gastric atrophy; blue column, patients without gastric atrophy. EI: eosinophilic infiltration**

non-EoE EGIDs with pathological gastric EI were uniformly observed in the stomach, with no specific trend in frequency or distribution depending on atrophic gastritis, a surrogate marker of *H. pylori* infection. Large or deep gastric ulcers with swollen/irregular margins might be characteristic of those found in non-EoE EGIDs and should be noted in the

**Table 3. Findings from Previous Studies on Clinical Characteristics of Active Gastric Ulcers in Patients with Non-EoE EGIDs.**

| Reference | Total no. of patients | Ulcer characteristics/complication | | | | | | | Location | | | *H. pylori* status |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Size[a] | Number | Depth[b] | Marginal swelling | Marginal irregularity | Bleeding | Infiltrating eosinophils (/HPF) | Antrum | Body | Both antrum and body | |
| 39 | 1 | Large | Single | Deep | Unknown | Unknown | - | Unknown | + | - | - | Negative (histology) |
| 40 | 1 | Large | Multiple | Unknown | Unknown | Unknown | - | ≥100 | - | - | + | Negative (histology) |
| 41 | 1 | Large | Multiple | Deep | + | + | - | Unknown | - | + | - | Negative (serum IgG antibody, rapid urease test) |
| 42 | 1 | Small | Multiple | Deep | + | - | - | 130 | + | - | - | Negative (serum IgG antibody) |
| 23 | 7 | Large (5) | Unknown | Deep (3) | +(3) | + (unknown) | - | Median 36 (30-70) | +(3) | +(2) | - | Unknown |
| | | Small (2) | Multiple (2) | Shallow (2) | - | + (unknown) | - | | +(2) | - | - | Unknown |
| 43 | 1 | Large | Multiple | Shallow | - | + | - | ≥100 | - | + | - | Post eradication |
| Our cases | 6 | Large (3) | Single (1)/ multiple (2) | Shallow (1)/ deep (2) | +(3) | +(2) | - | 70 (50-320) | - | +(3) | - | Post eradication (2), positive (1, serum IgG antibody) |
| | | Small (3) | Single (2)/ multiple (1) | Shallow (1)/ deep (2) | - | +(1) | - | 113 (31-603) | +(1) | +(2) | - | Negative (3, serum IgG antibody) |

[a]Large and small ulcers were defined as ulcers ≥ 2 cm and < 2 cm in diameter, respectively. Ulcer size was roughly assessed with reference to the presented endoscopy images in each report except when the size was explicitly stated, such as in the three reports by Scolapio et al. (39) (7cm), Kristopaitis et al. (40) (4 cm×3 cm), and Fujiwara et al. (23) (≥2 cm, vs. <2 cm).

[b]As shown in Figures 3, active ulcers with and without a distinct depth are defined as deep and shallow ulcers, respectively.

The value in parentheses is the number of the patients in each report manifesting each finding.

differential diagnosis of idiopathic peptic ulcers. Further prospective studies focusing on the endoscopic features and their association with histological findings are warranted. Future studies should directly investigate in detail the influence of *H. pylori* infection on gastric lesions in non-EoE EGIDs.

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

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## References

**1.** Gonsalves N. Eosinophilic gastrointestinal disorders. Clin Rev Allergy Immunol **7**: 272-285, 2019.

**2.** Dellon ES, Gonsalves N, Abonia JP, et al. International consensus recommendations for eosinophilic gastrointestinal disease nomenclature. Clin Gastroenterol Hepatol **20**: 2474-2484.e3, 2022.

**3.** Hirano I, Moy N, Heckman MG, Thomas CS, Gonsalves N, Achem SR. Endoscopic assessment of the oesophageal features of eosinophilic oesophagitis: validation of a novel classification and grading system. Gut **62**: 489-495, 2013.

**4.** Abe Y, Sasaki Y, Yagi M, et al. Endoscopic diagnosis of eosinophilic esophagitis: basics and recent advances. Diagnostics (Basel) **12**: 3202, 2022.

**5.** Chen MJ. Eosinophilic gastroenteritis: clinical experience with 15 patients. World J Gastroenterol **9**: 2813, 2003.

**6.** Zhang L, Duan L, Ding S, et al. Eosinophilic gastroenteritis: clinical manifestations and morphological characteristics, a retrospective study of 42 patients. Scand J Gastroenterol **46**: 1074-1080, 2011.

**7.** Kinoshita Y, Furuta K, Ishimura N, et al. Clinical characteristics of Japanese patients with eosinophilic esophagitis and eosinophilic gastroenteritis. J Gastroenterol **48**: 333-339, 2013.

**8.** Pesek RD, Reed CC, Collins MH, et al.; the Consortium of Eosinophilic Gastrointestinal Disease Researchers. Association between endoscopic and histologic findings in a multicenter retrospective cohort of patients with non-esophageal eosinophilic gastrointestinal disorders. Dig Dis Sci **65**: 2024-2035, 2020.

**9.** Sasaki Y, Abe Y, Mizumoto N, Nomura E, Ueno Y. Small bowel endoscopic features of eosinophilic gastroenteritis. Diagnostics (Basel) **13**: 113, 2022.

**10.** Kim HP, Vance RB, Shaheen NJ, Dellon ES. The prevalence and diagnostic utility of endoscopic features of eosinophilic esophagitis: a meta-analysis. Clin Gastroenterol Hepatol **10**: 988-996, 2012.

**11.** Yamamoto M, Nagashima S, Yamada Y, et al. Comparison of nonesophageal eosinophilic gastrointestinal disorders with eosinophilic esophagitis: a nationwide survey. J Allergy Clin Immunol Pract **9**: 3339-3349.e8, 2021.

**12.** Genta RM, Dellon ES, Turner KO. Non-oesophageal eosinophilic gastrointestinal diseases are undersuspected clinically and underdiagnosed pathologically. Aliment Pharmacol Ther **56**: 240-250, 2022.

**13.** Jessurun J. *Helicobacter pylori*: an evolutionary perspective. Histopathology **78**: 39-47, 2021.

**14.** al-Assi MT, Genta RM, Karttunen TJ, Graham DY. Ulcer site and complications: relation to *Helicobacter pylori* infection and NSAID use. Endoscopy **28**: 229-233, 1996.

**15.** Kim Y, Yokoyama S, Watari J, et al. Endoscopic and clinical features of gastric ulcers in Japanese patients with or without *Helicobacter pylori* infection who were using NSAIDs or low-dose aspirin. J Gastroenterol **47**: 904-911, 2012.

**16.** Iijima K, Ara N, Abe Y, et al. Biphasic effects of *H. pylori* infection on low-dose aspirin-induced gastropathy depending on the gastric acid secretion level. J Gastroenterol **47**: 1290-1297, 2012.

**17.** Iijima K, Kanno T, Abe Y, et al. Preferential location of idiopathic peptic ulcers. Scand J Gastroenterol **51**: 782-787, 2016.

**18.** Bhargava N, Venkateswaran S, Ramakrishna BS, Mathan M. Colonization by *Helicobacter pylori* and its relationship to histological changes in the gastric mucosa in portal hypertension. J Gastroenterol Hepatol **9**: 507-511, 1994.

**19.** Nishino K, Kawanaka M, Manabe N, Suehiro M, Kawamoto H, Haruma K. Portal hypertensive gastropathy in liver cirrhosis: prevalence, natural history, and risk factors. Intern Med **61**: 605-613, 2022.

**20.** Nakamura S, Matsumoto T, Kobori Y, Iida M. Impact of *Helicobacter pylori* infection and mucosal atrophy on gastric lesions in patients with familial adenomatous polyposis. Gut **51**: 485-489, 2002.

**21.** Ishihara S, Kinoshita Y, Schoepfer A. Eosinophilic esophagitis, eosinophilic gastroenteritis, and eosinophilic colitis: common mechanisms and differences between East and West. Inflamm Intest Dis **1**: 63-69, 2016.

**22.** Pesek RD, Greuter T, Lopez-Nunez O, Bernieh A, Straumann A, Collins MH. Clinicopathologic correlations in eosinophilic gastrointestinal disorders. J Allergy Clin Immunol Pract **9**: 3258-3266, 2021.

**23.** Fujiwara Y, Tanoue K, Higashimori A, et al.; F-Study group. Endoscopic findings of gastric lesions in patients with eosinophilic gastrointestinal disorders. Endosc Int Open **8**: E1817-E1825, 2020.

**24.** Kimura K, Takemoto T. An endoscopic recognition of the atrophic border and its significance in chronic gastritis. Endoscopy **1**: 87-97, 1969.

**25.** Kinoshita Y, Sanuki T. Review of non-eosinophilic esophagitis-eosinophilic gastrointestinal disease (non-EoE-EGID) and a case series of twenty-eight affected patients. Biomolecules **13**: 1417, 2023.

**26.** Hirano I, Collins MH, King E, et al.; CEGIR investigators. Prospective endoscopic activity assessment for eosinophilic gastritis in a multisite cohort. Am J Gastroenterol **117**: 413-423, 2022.

**27.** Mizokami Y, Narushima K, Shiraishi T, Otsubo T, Narasaka T, Matsuoka T. Non-Helicobacter pylori ulcer disease in rheumatoid arthritis patients receiving long-term NSAID therapy. J Gastroenterol **35** Suppl 1: 38-41, 2000.

**28.** Kamada T, Hata J, Kusunoki H, et al. Endoscopic characteristics and *Helicobacter pylori* infection in NSAID-associated gastric ulcer. J Gastroenterol Hepatol **21**: 98-102, 2006.

**29.** Fukuzawa M, Kawai T, Watanabe M, Tomiyama H, Yamashina A, Moriyasu F. Correlation between *Helicobacter pylori* infection and low-dose aspirin use on damage of the upper gastrointestinal tract. J Gastroenterol Hepatol **27** Suppl 3: 76-81, 2012.

**30.** Joo JY, Cho JM, Yoo IH, et al. Eosinophilic gastroenteritis as a cause of non-*Helicobacter pylori*, non-gastrotoxic drug ulcers in children. BMC Gastroenterol **20**: 280, 2020.

**31.** Almadi MA, Lu Y, Alali AA, Barkun AN. Peptic ulcer disease. Lancet **404**: 68-81, 2024.

**32.** Kanno T, Iijima K, Abe Y, et al. A multicenter prospective study on the prevalence of *Helicobacter pylori*-negative and nonsteroidal anti-inflammatory drugs-negative idiopathic peptic ulcers in Japan. J Gastroenterol Hepatol **30**: 842-848, 2015.

**33.** Sugawara K, Koizumi S, Horikawa Y, et al. Is the new potent acid-inhibitory drug vonoprazan effective for healing idiopathic peptic ulcers? A multicenter observational study in Akita Prefecture, Japan. J Gastroenterol **54**: 963-971, 2019.

**34.** Nakajima N, Takeuchi T, Hokari R, et al. Background factors of idiopathic peptic ulcers and optimal treatment methods: a multicenter retrospective Japanese study. J Clin Biochem Nutr **74**: 82-89, 2024.

**35.** Yamane T, Ishii T, Umeda A, Shimao H. Evaluation of six cases of idiopathic gastric antral ulcer. Gastroenterology Res **5**: 120-126, 2012.

**36.** Miyake K, Tanikawa T, Haruma K, et al. A case of idiopathic peptic ulcer disease treated effectively with trimebutine maleat. Acta Med Okayama **78**: 85-88, 2024.

**37.** Iwamuro M, Tanaka T, Kawano S, Kawahara Y, Otsuka M. Idiopathic gastric antral ulcers. Intern Med **63**: 1367-1371, 2024.

**38.** Kanno T, Iijima K, Abe Y, et al. *Helicobacter pylori*-negative and non-steroidal anti-inflammatory drugs-negative idiopathic peptic ulcers show refractoriness and high recurrence incidence: multicenter follow-up study of peptic ulcers in Japan. Dig Endosc **28**: 556-563, 2016.

**39.** Scolapio JS, DeVault K, Wolfe JT. Eosinophilic gastroenteritis presenting as a giant gastric ulcer. Am J Gastroenterol **91**: 804-805, 1996.

**40.** Kristopaitis T, Neghme C, Yong SL, Chejfec G, Aranha G, Keshavarzian A. Giant antral ulcer: a rare presentation of eosinophilic gastroenteritis - case report and review of the literature. Am J Gastroenterol **92**: 1205-1208, 1997.

**41.** Katsumi N, Yamaguchi Y, Yamato T, et al. Multiple ulcerative lesions of the stomach: a rare case of eosinophilic gastroenteritis. Gastrointest Endosc **56**: 762-764, 2002.

**42.** Tomizawa T, Kawamura O, Kusano M. A case of proton pump inhibitor-resistant multiple gastric ulcers caused by eosinophilic gastroenteritis. Clin Gastroenterol Hepatol **13**: A23-A24, 2015.

**43.** Iwamuro M, Murakami T, Tanaka T, et al. Eosinophilic gastritis in a patient previously treated with dupilumab. Case Rep Gastrointest Med **2020**: 6381670, 2020.

**44.** Ohmiya N, Saga S, Ohbayashi M, et al. Kinetics and collagenolytic role of eosinophils in chronic gastric ulcer in the rat. Histochem Cell Biol **108**: 27-34, 1997.

**45.** Otani Y, Sakurai Y, Kameyama K, et al. Matrix metalloproteinase gene expression in chronic gastric ulcer: a potential role of eosinophils in perforation. J Clin Gastroenterol **25** Suppl 1: S101-S104, 1997.

**46.** Dellon ES, Gonsalves N, Rothenberg ME, et al. Determination of biopsy yield that optimally detects eosinophilic gastritis and/or duodenitis in a randomized trial of lirentelimab. Clin Gastroenterol Hepatol **20**: 535-545, 2022.

**47.** Iijima K, Sekine H, Koike T, Imatani A, Ohara S, Shimosegawa T. Long-term effect of Helicobacter pylori eradication on the reversibility of acid secretion in profound hypochlorhydria. Aliment Pharmacol Ther **19**: 1181-1188, 2004.