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Original article

Eosinophil infiltration in the upper gastrointestinal tract of patients with bronchial asthma

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Abbreviations:
GI, gastrointestinal; PPIs, proton pump inhibitors; EGE, eosinophilic gastroenteritis; EoE, eosinophilic esophagitis; BA, bronchial asthma;
EGD, esophagogastroduodenoscopy;
EGPA, eosinophilic granulomatosis with polyangiitis

ABSTRACT

Background: Eosinophilic esophagitis (EoE) is related to allergic diseases such as bronchial asthma (BA), atopic dermatitis, and allergic rhinitis. The aim of this study was to examine the eosinophil infiltration in the upper gastrointestinal (GI) tract in patients with BA using esophagogastroduodenoscopy.
Methods: Patients with BA who had upper GI tract symptoms were enrolled. Patients who received systemically administered steroids were excluded. Eosinophil infiltrations in the esophagus, stomach, and duodenum were examined with regard to the endoscopic findings and pathological findings of biopsy specimens (UMIN000010132).
Results: Ninety patients were enrolled from October in 2012 to September in 2014. Thirty-six were male, 54 were female, and the mean age was 57.5 years. Eighty-one (90%) used inhaled corticosteroids. Fourteen patients (15.6%) had reflux esophagitis, 8 of whom had grade A and 6 had grade B. No patient with EoE was observed. One female patient who had marked eosinophil infiltration in the esophagus, stomach, and duodenum was diagnosed as having eosinophilic gastroenteritis, but endoscopy showed only mucosal edema in the antrum. Another female patient who had marked eosinophil infiltration in the esophagus, stomach, and duodenum was diagnosed as having eosinophilic granulomatosis with polyangiitis, and endoscopy showed erosions in the antrum and the duodenum. Three patients had eosinophil infiltration in the stomach, but none of them had severe symptoms.
Conclusions: Patients with asthma who had upper gastrointestinal symptoms rarely had eosinophilic gastrointestinal disorders. Biopsy specimens are of high importance in the diagnosis of eosinophilic gastrointestinal disorders even if there is no remarkable endoscopic finding.

Introduction

Eosinophilic esophagitis (EoE) and eosinophilic gastroenteritis (EGE) are rare pathological conditions characterized by dense infiltration of eosinophils in esophagogastrointestinal mucosa.[1,2] When eosinophil infiltration is demonstrated only in the esophageal epithelial layer, the pathological condition is called EoE. On the other hand, when it is found in gastric and/or intestinal/colonic mucosa irrespective of esophageal involvement, it is called EGE. Affected patients develop esophageal fibrostenotic complications after chronic inflammation and often suffer from dysphagia, swallowing discomfort, and heartburn.[3–5] Patients with EGE have abdominal pain and diarrhea, high peripheral eosinophil counts, and gastrointestinal wall thickening identifiable in CT images. The prevalence of EoE has been reported to be increasing rapidly in Western countries.[6–9] Straumann *et al.*[1] reported that in Switzerland it increased from 2/100,000 in 1989 to 23/100,000 in 2004. Similarly, Prasad *et al.*[9] found that in the US it was 55/100,000 in 2006 and that the incidence of clinically diagnosed EoE has increased markedly over the last 3 decades, whereas the prevalence and incidence of EGE have not been fully clarified. The prevalence of EoE was calculated to be 17.1/100,000 in the Japanese population,[10]

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and EGE is more prevalent than EoE.[11] The prevalence of EoE in endoscopy-examined cases was recently reported in the USA to be 6.5%.[12] EoE cases are frequently associated with allergic diseases such as bronchial asthma (BA), atopic dermatitis, allergic rhinitis, and various food or drug allergies. Approximately 30–50% of individuals with EoE have asthma, whereas only 10% of the general population does.[13,14] Similarly, 50–75% have allergic rhinitis, and only 39% of healthy children do. In addition, 10–20% of children with EoE have IgE-mediated food allergies (urticaria and anaphylaxis), whereas only 1–5% of normal children does.[5,13,14] These rates of atopy (asthma, allergic rhinitis, and atopic dermatitis) are approximately three times higher than what is expected in the general population. Also, approximately 30–50% of individuals with EGE have allergic diseases like EoE.[15,16]

This study was to examine the eosinophil infiltration in the upper gastrointestinal (GI) tract in patients with BA by using esophagogastroduodenoscopy (EGD).

Methods

Ninety patients (36 male and 54 female) with BA who had upper GI symptoms and underwent EGD in our hospital were enrolled in this study. Patients treated with systemically administered steroids were excluded, but those taking only inhaled steroids were not. Their ages ranged from 16 to 78 years, and the mean age was 57.5 years. Eighty-one patients (90.0%) took inhaled corticosteroids, 14 (15.6%) took proton pump inhibitors, and 2 (2.2%) took H_2 receptor antagonists. Twenty-nine patients (32.2%) had allergic rhinitis, 8 (8.9%) had atopic dermatitis, and 5 (5.6%) had food allergies (Table 1).

Upper GI symptoms were examined using a frequency scale for symptoms of gastroesophageal disease (F-scale).[17] EGD was conducted, and hiatal hernia was assessed using Makuuchi's classification[18] and reflux esophagitis was assessed using the Los Angeles classification.[19] A circular ring, longitudinal furrow, white exudate, or stenosis in the esophagus was observed as a characteristic finding in EoE. Moreover, edema, marked redness, erosion, or ulcer in the stomach was observed as an endoscopic finding in EGE, although those were not specific for EGE. Biopsy specimens were taken at the upper, middle, and lower body of the esophagus and at the gastric body and antrum and at the bulbus of the duodenum. Eosinophilic infiltration was histologically diagnosed as more than 15 eosinophils in a high-power field.

The study protocol was in accordance with the tenets of the revised Declaration of Helsinki (1989) and was approved by the institutional review boards at our institutions. Written informed consent was obtained from all the patients. This study was registered with the UMIN Clinical Trials Registry (UMIN000010132).

Results

The questionnaire of upper GI symptoms was examined in 72 patients (80%).

Table 1
Clinical characteristics of patients.

Male/Female	36/54
Mean age	57.5 (16–78)
Inpatients/Outpatients	6/84
Medication	
Inhalant corticosteroids	81 (90.0%)
Proton pump inhibitor	14 (15.5%)
H_2 receptor antagonist	2 (2.2%)
Allergic disease	
Allergic rhinitis	29 (32.2%)
Atopic dermatitis	8 (8.9%)
Food allergy	5 (5.6%)

Table 2
Upper gastrointestinal symptoms.

Heart burn	62 (86.1%)
Bloating	63 (87.5%)
Feeling heavy after meals	65 (90.3%)
Subconsciously rubbing your chest	43 (60.9%)
Feeling sick after meals	21 (29.2%)
Heart burn after meals	20 (27.8%)
Unusual sensation in your throat	25 (34.7%)
Feeling full while eating meals	23 (31.9%)
Stucking when you swallow	25 (34.7%)
Bitter liquid coming up into your throat	61 (84.7%)
Burping a lot	62 (86.1%)
Heart burn when you bend over	18 (25.0%)
Epigastralgia	13 (18.1%)

Sixty-two patients (89.9%) had heartburn, 63 patients (87.5%) had bloating, 65 patients (90.3%) had a heavy feeling after meals, 43 patients (59.7%) subconsciously rubbed their chest, 61 patients (84.7%) had bitter liquid coming up into the throat, and 62 patients (86.1%) had a lot of burping. Twenty-five patients (34.7%) had food sticking when swallowing. Only thirteen patients (18.1%) had epigastralgia (Table 2). The mean F-scale score was 9.0 (1–34), and 32 patients (44.4%) had an F-scale score greater than 8.

Eighty patients (88.9%) had hiatal hernia, 14 of whom had grade A, 65 of whom had grade B, and one had grade C. Fourteen patients (15.6%) had reflux esophagitis, 8 of whom had grade A and 6 of whom had grade B, however, all had mild reflux esophagitis. A circular ring, longitudinal furrow, white exudate, or stenosis in the esophagus was not observed in any patient. Edema in the stomach was observed in one patient, marked redness was observed in one patient, and erosions were observed in one patient.

One patient, a 69-year-old female was diagnosed as having EGE because she had severe epigastralgia, eosinophilia (1,825/μL) and BA, which was treated with inhaled corticosteroids. EGD showed no abnormal findings in the esophagus and the duodenum and showed mild edema in the gastric antrum (Fig. 1). The pathological findings in any location, however, showed eosinophil infiltration (Fig. 2a, b). She has been improved by administration of oral corticosteroids.

Another patient, a 16-year-old female who had precedent BA that was treated with inhaled corticosteroids was diagnosed as

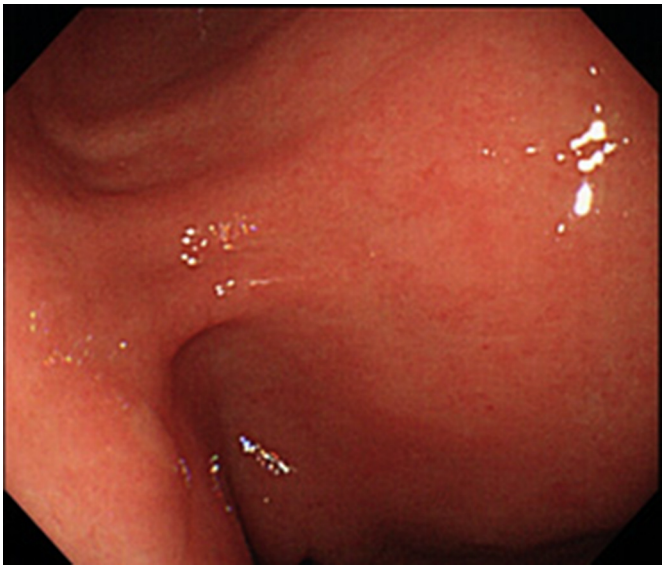

Fig. 1. Mild edema in the antrum.

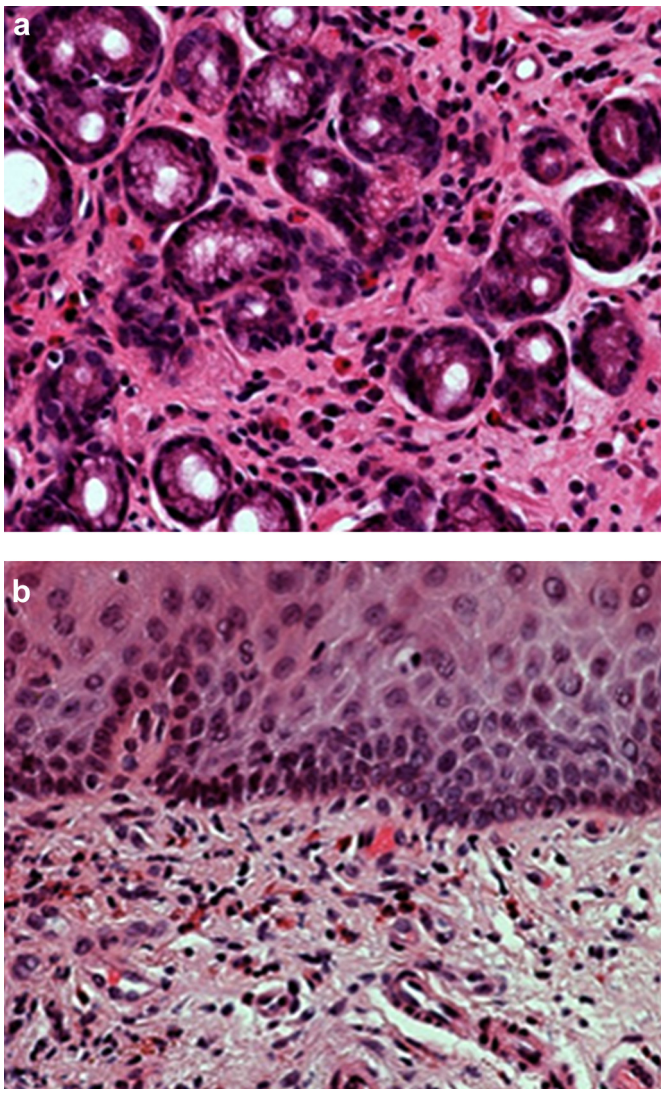

Fig. 2. **a**: Eosinophil infiltration in the antral mucosa. **b**: Eosinophil infiltration in the esophageal mucosa.

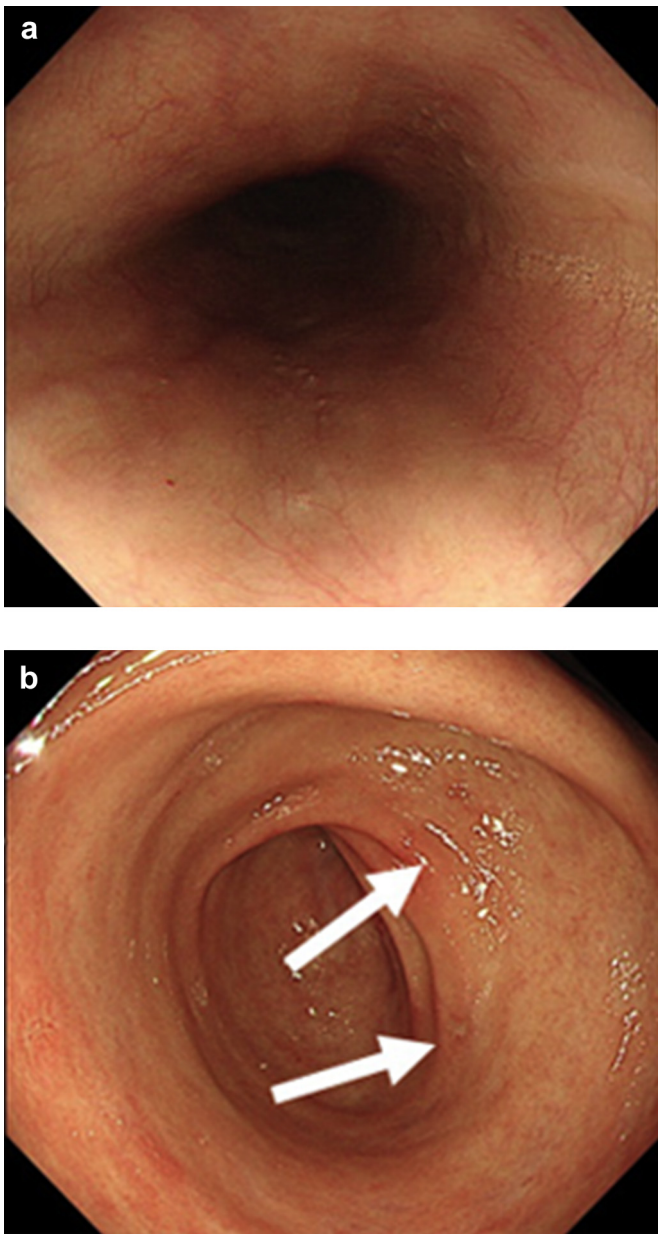

Fig. 3. **a**: No specific findings for EoE in the esophagus. **b**: Erosions in the antrum.

having eosinophilic granulomatosis with polyangiitis (EGPA) because she had severe epigastralgia, marked eosinophilia (3,510/μL), and a skin eruption. EGD showed no abnormal findings in the esophagus (Fig. 3a) but showed erosions in the gastric antrum and the duodenum (Fig. 3b). The pathological findings in any location showed eosinophil infiltration (Fig. 4a, b). The pathological findings of biopsy specimens of the skin eruption showed vasculitis in the small arteries. She has been improved by administration of oral corticosteroids.

Moreover, three patients with eosinophilic infiltration to the stomach were detected, but EGD showed no abnormal findings in the stomach, and all of them had no eosinophilia. They were not diagnosed as having EGE because their upper GI symptoms were mild and spontaneously improved thereafter.

Discussion

Kusano *et al.*[17] have reported that when the cutoff score was set at 8 points, F-scale showed a sensitivity of 62%, a specificity of 59%, and an accuracy of 60%. In our study, 32 of 72 patients with upper GI symptoms (44.4%) had an F-scale score greater than 8. Most of them were thought to have GERD. Eighty patients (88.8%) had hiatal hernia regardless the level. Moreover, 14 patients (15.6%) had mild reflux esophagitis. According to the Montreal definition and classification of GERD,[20] BA is associated with GERD and it is one of the extraesophageal syndromes caused by GERD. However, the symptoms of EoE are sometimes similar to those of GERD. Endoscopic and pathological examinations are necessary for differentiation between EoE and GERD.

Approximately 30–50% of individuals with EoE have BA.[12] The mechanisms of EoE might be similar to BA,[21,22] but no patient with EoE was detected among patients with BA in our study. Our study had a small sample size and it was conducted in a single institution. On the other hand, the standard treatment for BA is inhalation of corticosteroids and severe BA is treated by systemic administration of corticosteroids.[23] Patients treated systemically administered corticosteroids were excluded from our study, but those taking only inhaled corticosteroids were not. In our study, most patients with

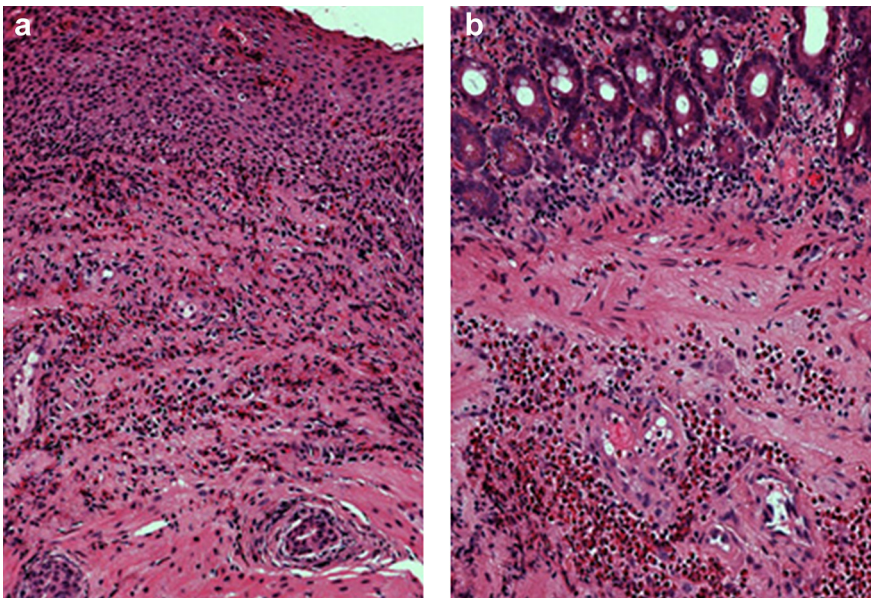

Fig. 4. **a**: Eosinophil infiltration in the esophageal mucosa. **b**: Eosinophil infiltration in the antral mucosa.

BA (90%) took inhalant corticosteroids. All of an inhalant corticosteroid dose should be inhaled, but a bit of it might be swallowed. The standard treatment for EoE is swallowing of inhaled corticosteroids in spite of coexistence of BA.[1–5] Systematic administration of corticosteroids is typically reserved when topical steroids are not effective or patients need a rapid improvement in symptoms.[24] Even if the amount of swallowed inhalant corticosteroids is small, it might prevent the occurrence of EoE. Harer *et al.*[25] have reported that the use of inhaled corticosteroids was negatively associated with EoE for asthma patients, and that one of the intriguing findings was the possible protective effect of inhaled steroids on having EoE. This might be why no patients with EoE were observed in our study. However, this incidental swallowing is unlikely to deliver the level of steroid doses delivered directly to the esophageal mucosa that are used to treat EoE.

In our study, the number of biopsy specimens in the esophagus was three, but in the Western countries more than four biopsy specimens from the mid and distal esophagus are recommended to make a diagnosis of eosinophil infiltration in the esophagus.[26] Eosinophil-predominant inflammation on esophageal biopsy characteristically consists a peak value of more than 15 eosinophils per high power field.[24] Eosinophil infiltration in the esophagus could not be detected, because the number of biopsy specimens might not be sufficient.

Recently, it has been reported that some patients with symptoms suggestive of EoE have endoscopic features of EoE, however, their symptoms and esophageal eosinophilia resolve after a PPI course.[27] It is now termed PPI-responsive esophageal eosinophilia. It is not necessary to take inhaled corticosteroids if the patient's symptoms are improved by PPI. The prevailing hypothesis to explain PPI-responsive esophageal eosinophilia has been that coexisting GERD might be the priming event, allowing the potential entry of food derived allergenic molecules through acid-induced epithelial barrier damage. Thus, GERD-induced epithelial damage could expose the deeper layers of the esophageal squamous epithelium to antigens that ordinarily could not penetrate a normal mucosa.[28] In our study, 14 patients (15.6%) took PPI, therefore, PPI might prevent EoE in those patients.

One patient who took inhalant corticosteroids was diagnosed as having EGE. Eosinophil infiltration was detected not only in the stomach and duodenum but also in the esophagus. The inhalant corticosteroids could not prevent the occurrence of EGE. The clinical features of EGE are related to the location, extent, and layer of bowel with eosinophil infiltration, and EGE has three subtypes: mucosal disease, muscular-layer disease, and subserosal disease.[29] This patient had mucosal disease without ascites, but endoscopy showed only mild edema in the antrum. Biopsy specimens are necessary to make a diagnosis of eosinophil infiltration for those patients even if endoscopy does not show abnormal findings.

EGPA, formerly named Churg–Strauss syndrome is a rare systemic small- and medium-sized vessel vasculitis, with severe BA and blood and tissue eosinophilia. The classification criteria include 4 out of 6; asthma, eosinophilia, history of allergy, pulmonary infiltrates, paranasal abnormalities and extravascular eosinophils. Approximately 30–50% of patients with EGPA have been reported to have involvement of the gut.[30] In our study, one patient who took inhalant corticosteroids was diagnosed as having EGPA. Eosinophil infiltration was detected not only in the stomach and duodenum but also in the esophagus. The inhalant corticosteroids could not prevent the occurrence of EGPA. Endoscopy showed mild erosions in the antrum and duodenum. Biopsy specimens are necessary to make a diagnosis of eosinophil infiltration for those patients.

Three patients with eosinophil infiltration in the stomach were detected but they were not diagnosed as having EGE because their upper GI symptoms were mild and improved thereafter. The eosinophil infiltration in the stomach might be spontaneous and temporary due to food allergies. Follow-up examination is needed.

There are some limitations in this study. As the sample size was too small, a large multicenter trial is expected in near future. Patients treated not only systemically administered corticosteroids but also inhaled corticosteroids are needed to be excluded. However, it seems to be difficult to enroll those patients. The number of appropriate biopsy specimens in the esophagus must be determined.

In conclusion, patients with asthma who had upper gastrointestinal symptoms rarely had eosinophilic gastrointestinal disorders. Biopsy specimens are of high importance in the diagnosis of eosinophilic gastrointestinal disorders even if there is no remarkable endoscopic finding.

Conflict of interest

The authors have no conflict of interest to declare.

Authors' contributions

HI designed the study and wrote the manuscript. MY, HO, KY, TK, TN, YU, TS and MN contributed to data collection. HI, MY, HO and KY performed esophagogastroduodenoscopy. HK performed pathological examination. MK, HN and MN supervised this study. All authors read and approved the final manuscript.

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