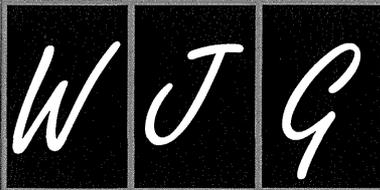


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Systematic review: Eosinophilic esophagitis in Asian countries

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Abstract

AIM: To investigate the prevalence and the clinical characteristics of Asian patients with eosinophilic esophagitis.

METHODS: We conducted a systematic search of the PubMed and Web of Science databases for original studies, case series, and individual case reports of eosinophilic esophagitis in Asian countries published from January 1980 to January 2015. We found 66 and 80 articles in the PubMed and Web of Science databases, respectively; 24 duplicate articles were removed. After excluding animal studies, articles not written in English, and meeting abstracts, 25 articles containing 217 patients were selected for analysis.

RESULTS: Sample size-weighted mean values were determined for all pooled prevalence data and clinical characteristics. The mean age of the adult patients with eosinophilic esophagitis was approximately 50 years, and 73% of these patients were male. They frequently presented with allergic diseases including bronchial asthma, allergic rhinitis, food allergy, and atopic dermatitis. Bronchial asthma was the most frequent comorbid allergic disease, occurring in 24% of patients with eosinophilic esophagitis. Dysphagia was the primary symptom reported; 44% of the patients complained of dysphagia. Although laboratory blood tests are not adequately sensitive for an accurate diagnosis of eosinophilic esophagitis, endoscopic examinations revealed abnormal findings typical of this disease, including longitudinal furrows and concentric rings, in 82% of the cases. One-third of the cases responded to proton pump inhibitor administration.

CONCLUSION: The characteristics of eosinophilic

esophagitis in Asian patients were similar to those reported in Western patients, indicating that this disease displays a similar pathogenesis between Western and Asian patients.

Key words: Eosinophilic esophagitis; Allergy; Prevalence; Symptom; Endoscopy; Asia; Treatment

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Core tip: We conducted a systematic literature search of eosinophilic esophagitis in Asian countries. More than 200 patients with eosinophilic esophagitis were found, and their clinical characteristics were summarized. All clinical characteristics of the Asian patients, except for the prevalence of food impaction, were similar to those of Western patients. Eosinophilic esophagitis may share the same pathogenetic mechanisms between Asian and Western patients.

Kinoshita Y, Ishimura N, Oshima N, Ishihara S. Systematic review: Eosinophilic esophagitis in Asian countries. *World J Gastroenterol* 2015; 21(27): 8433-8440 Available from: URL: <http://www.wjgnet.com/1007-9327/full/v21/i27/8433.htm> DOI: <http://dx.doi.org/10.3748/wjg.v21.i27.8433>

INTRODUCTION

Eosinophilic esophagitis (EoE) is a chronic inflammatory esophageal disease that induces dense intra-epithelial infiltration of eosinophils in the esophageal mucosa^[1,2]. Affected patients develop esophageal fibrostenotic complications after chronic inflammation and often suffer from dysphagia, swallowing discomfort, and heartburn. More than half of patients with EoE have concomitant atopic diseases, which may play a role in its development. The pathogenetic mechanism of EoE is considered to be a Th2-type chronic allergic reaction, primarily to food allergens, and IL-5, -13, and -15, eotaxin-3, periostin, and TGF- β are considered to be the principal participants in the development of EoE^[3,4]. As with many allergic diseases, including bronchial asthma, the incidence and the prevalence of EoE have been shown to be rapidly increasing, with a reported incidence in Western countries ranging from 10 to 50 per 100000 individuals in the general population^[5].

Published reports of EoE from Asian countries are limited, including only observational studies using a small sample size and case reports. Because of this limited information, the prevalence of EoE in Asian countries, as well as similarities and differences in regards to the clinical characteristics of affected patients, in Western and Asian countries have not been clarified. In the present study, we surveyed original publications and case reports of EoE from Asian countries and performed a systematic review.

MATERIALS AND METHODS

Systematic literature search

Systematic searches of PubMed and Web of Science for reports published from January 1980 to January 2015 were conducted using the following search strings: [eosinophilic esophagitis] and ([Asia] or [Asian] or [Japan] or [Japanese] or [Korea] or [Korean] or [China] or [Chinese] or [Taiwan] or [India] or [Indian] or [Indonesia] or [Cambodia] or [Singapore] or [Sri Lanka] or [Thailand] or [Nepal] or [Pakistan] or [Bangladesh] or [Timor] or [Bhutan] or [Philippines] or [Brunei] or [Viet Nam] or [Malaysia] or [Myanmar] or [Maldives] or [Mongolia] or [Laos]). All articles written in English, including original articles, case series, and individual case reports, were analyzed.

Data extraction and analysis

Because we were interested in the prevalence and the clinical characteristics of EoE in Asian countries, we focused on the number of cases investigated *via* upper gastrointestinal endoscopy. In addition, we recorded possible accompanying atopic diseases, symptoms, laboratory test results, endoscopic findings, and therapeutic responses.

Statistical analysis

Sample size-weighted mean values were determined for all pooled prevalence data and clinical characteristics. The statistical methods of this study were reviewed by Akira Yasuda, Department of Medical Informatics, Shimane University, Izumo, Japan.

RESULTS

Literature search

The literature search identified 25 articles, including 8 case reports, that fulfilled the inclusion criteria for this review (Figure 1)^[6-30]. Most studies were performed in Japan ($n = 15$), followed by Korea, Turkey, Saudi Arabia, China, and Taiwan. We did not find any reports from other Asian countries, including central and western Asian countries.

Demographic characteristics

The identified reports included a total of 217 Asian patients with EoE, of whom 73% were male. All studies except for 2 contained more males than females, although one report of 4 patients did not indicate their age or gender. The age of the patients in these studies ranged from 1 to 83 years, with a mean age of 40.4 years, and the mean age of the adult patients was approximately 50 years (Figure 2).

Prevalence of EoE

Nine studies investigated the prevalence of EoE in upper gastrointestinal cases investigated *via* endoscopy. Of 117946 cases in which endoscopy was used, EoE was

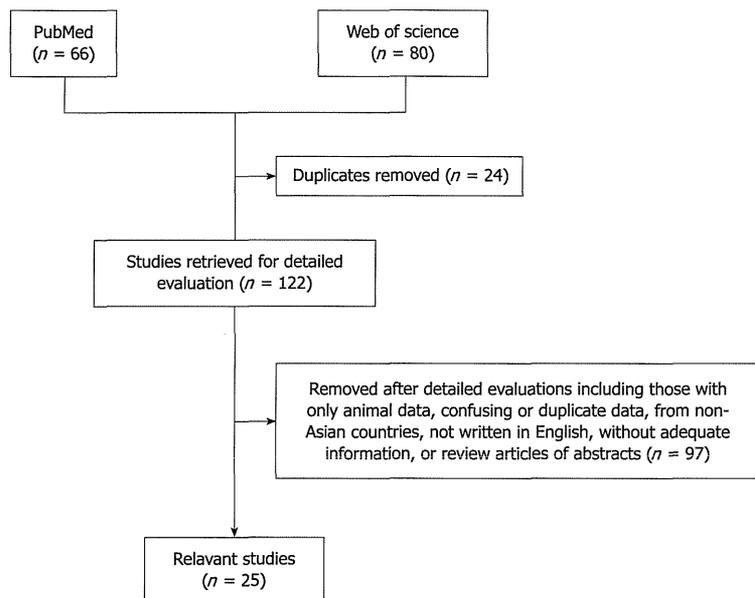


Figure 1 Flow chart of our systematic literature search.

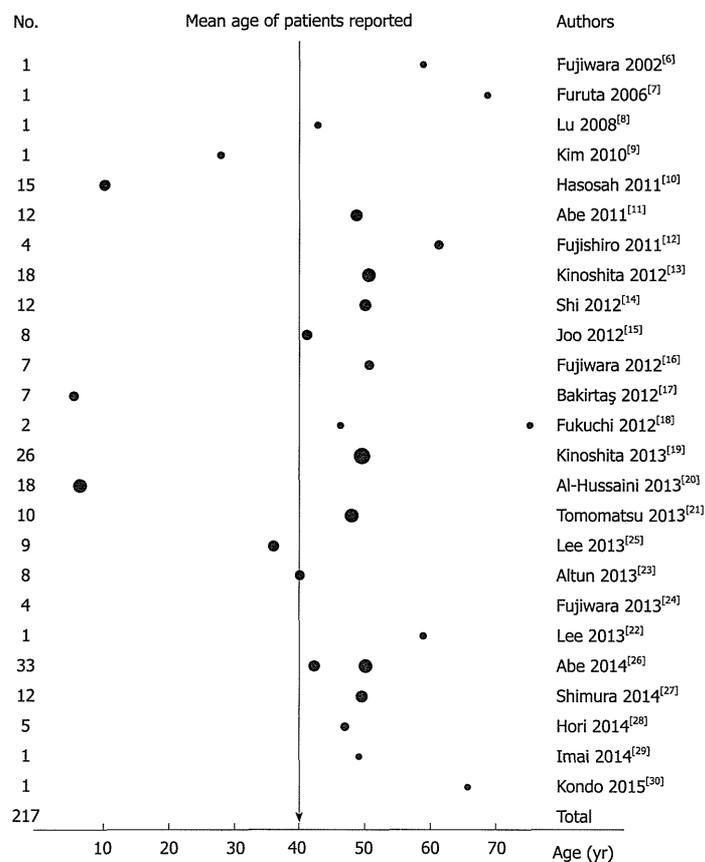


Figure 2 Number of patients with eosinophilic esophagitis in all 25 studies included in this review. The dots indicate the mean age, and the dot size indicates the number of patients. One report did not describe the ages of the included patients.

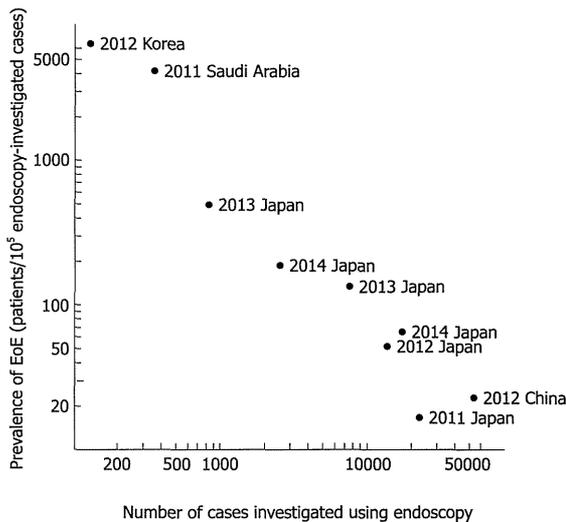


Figure 3 Reported prevalence of eosinophilic esophagitis in patients examined via upper gastrointestinal endoscopy. In the studies using a smaller sample size, the prevalence of eosinophilic esophagitis (EoE) was higher. Different indication criteria for endoscopic examination between institutions may be partially responsible for the large variation in the reported incidence of EoE.

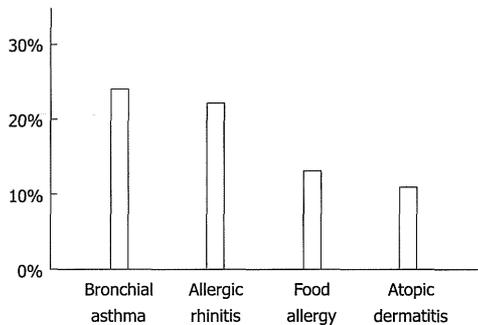


Figure 4 Allergic diseases reported by patients with eosinophilic esophagitis. Twenty-one articles contained descriptions of the histories of allergic diseases among the reported patients. The most frequently reported allergic disease was bronchial asthma, followed by allergic rhinitis.

found in 77 cases. The reported prevalence of EoE in these studies displayed wide variability, from 17 to 6557 per 10^5 endoscopy-investigated cases. However, the possibility of inclusion bias in the studies using a small sample size should be considered, as the studies using a small sample size showed a higher prevalence of EoE (Figure 3). Two studies that included more than 20000 endoscopy-investigated cases showed an EoE prevalence of approximately 20 in 10^5 cases, suggesting a lower prevalence in Asian countries than in Western countries. No studies investigated the population-based prevalence or incidence of EoE in Asian countries.

History of allergic diseases

A history of allergic diseases was reported for 175

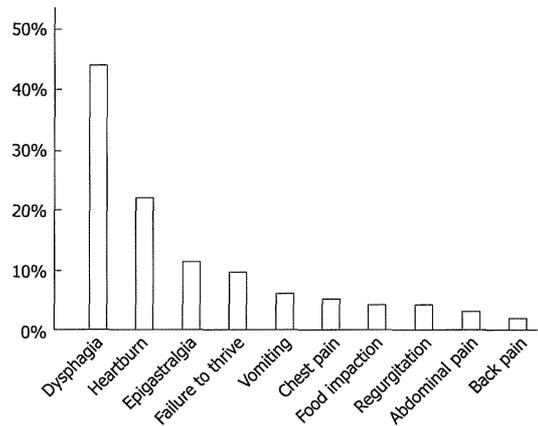


Figure 5 Symptoms reported by patients with eosinophilic esophagitis. Twenty-four articles contained descriptions of symptoms reported by patients. The most frequently reported symptom was dysphagia, followed by heartburn.

cases (Figure 4). Bronchial asthma was reported in 42 patients, allergic rhinitis in 39 patients, food allergies in 23 patients, and atopic dermatitis in 20 patients. More than 50% of the patients with EoE had some type of allergic disease or a medical history of an allergic disease.

Symptoms reported by patients

Symptoms were reported in 213 cases (Figure 5), and multiple symptoms were often noted. Dysphagia and/or swallowing discomfort, the most frequently noted symptoms, were reported by 93 patients. Other reported symptoms included heartburn ($n = 47$), epigastralgia ($n = 24$), failure to thrive ($n = 20$, only pediatric cases), vomiting ($n = 13$), chest pain ($n = 11$), food impaction ($n = 9$), regurgitation ($n = 8$), abdominal pain ($n = 6$), and back pain ($n = 4$). Of the 40 pediatric cases, 18 reported dysphagia or swallowing discomfort.

Laboratory test results

The possible presence of peripheral blood eosinophilia was reported in 102 patients, 34 (33%) of whom had eosinophilia (> 500 eosinophils/ μL), although high-grade eosinophilia (> 1000 eosinophils/ μL) was rarely encountered. The total serum IgE concentration was reported for 76 cases, of which 45 (59%) of the cases displayed elevated IgE levels.

Serum anti-*Helicobacter pylori* (*H. pylori*) IgG antibody levels were reported for 24 patients, although only 4 (17%) were found to be infected by *H. pylori*, suggesting a lower rate of infection in EoE cases than in healthy individuals.

Endoscopy

Endoscopic findings were reported for 188 patients (Figure 6), of whom 154 (82%) had some endoscopic abnormalities suggesting the presence of EoE,

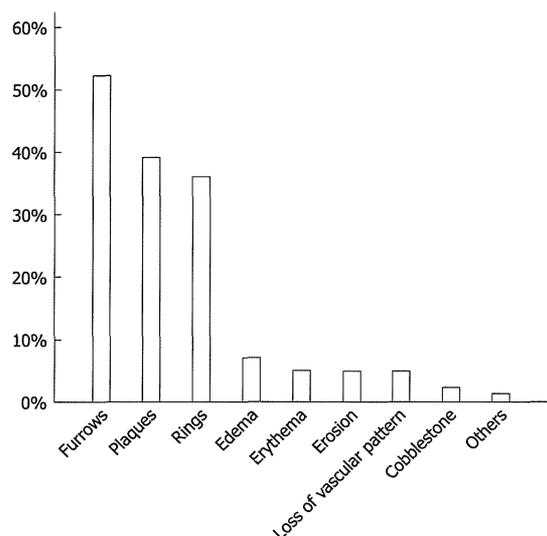


Figure 6 Endoscopic abnormalities found in patients with eosinophilic esophagitis. Longitudinal furrows, white plaques, and fixed/transient concentric rings were most frequently detected.

including furrows, concentric rings, and white plaques. Longitudinal furrows were the most frequently reported abnormality, observed in 52% of the patients, followed by white plaques and concentric rings. Shimura and co-workers investigated the sensitivity and the specificity of various endoscopic abnormalities in Asian patients and found that longitudinal furrows corresponded to the highest positive and negative predictive values^[27]. Non-specific findings such as edema, erythema, and decreased visibility of the vasculature were reported in a small number of patients.

Regarding the histological diagnosis of EoE, 7 studies employed 20 or 24 eosinophils/high power field as the minimal threshold to indicate eosinophil infiltration for EoE diagnosis. In the remaining studies, the patients were diagnosed with histological EoE when 15 or more eosinophils/high power field were found in esophageal mucosa biopsy specimens. Eosinophil micro-abscess, fibrosis in the esophageal sub-epithelial layer, and infiltration of other immunocytes into the epithelial layer have been reported to be possible characteristic histological findings of EoE, although these histological abnormalities were not used for the diagnosis of EoE in the collected publications. Additionally, the sites of biopsy sampling were not clearly described in the collected publications, despite that the sampling site may affect the sensitivity and the specificity of histological diagnosis.

Therapeutic response

Topical glucocorticoid therapy, elemental or elimination diet, and proton pump inhibitor (PPI) therapy were generally employed for the treatment of EoE. Some studies included PPI-responsive cases, whereas others excluded such cases. In 7 studies that included

PPI-responsive cases, 23 of the 61 patients (38%) responded favorably to PPI administration and were diagnosed with PPI-responsive EoE (PPI-REE) according to the 2011 Eosinophilic Esophagitis Updated Consensus Recommendations^[1].

All symptomatic patients with EoE were reported to be successfully treated *via* glucocorticoid or PPI administration or dietary therapy. A small number of patients had negligible symptoms that did not require therapeutic intervention or experienced spontaneous disease remission, at least temporarily, without any treatment. None of the reported patients required balloon dilatation treatment for esophageal stenosis.

DISCUSSION

Our review of the literature identified over 200 patients with EoE in Asian countries during the search period. An increasing trend of publication was observed since 2011, as 21 of the 25 studies surveyed were published after 2011. The age and gender ratios of the reported cases in Asian countries were very similar to those reported in Western countries^[1,2,31], although the reason for the male preponderance of EoE has yet to be clarified.

The prevalence of EoE in Asian countries has not been appropriately investigated *via* population studies, in contrast to the studies performed in Western countries^[5,32]. The prevalence of cases that utilized endoscopy varied remarkably among the studies reviewed here (Figure 3), and this variability may be partially due to the different indications for which upper gastrointestinal endoscopy is used and partially because of different levels of familiarity with EoE among endoscopists in different countries. In Western countries, EoE has been reported to be found in approximately 1 out of 200 endoscopy examinations^[33,34]. In contrast, studies using large a sample size performed in Asian countries have reported EoE in approximately 1 out of 5000 endoscopy examinations, indicating a much lower prevalence of EoE^[12,14]. Because the accessibility of and the indication for endoscopic examination are known to differ between Western and Asian countries, a direct comparison of the EoE prevalence based on endoscopic findings between these 2 regions of the world is difficult. We believe that population-based studies in Asian countries are needed.

Similar to Western EoE patients, Asian EoE patients frequently presented with comorbid atopic and allergic diseases^[1,2,31]. In both regions, bronchial asthma has been shown to be the allergic disease most frequently associated with EoE. Thus, the atopic condition is considered to be at least partially involved in the development of EoE not only in Western countries but also in Asian countries. The occurrence of allergic diseases may be prevented by bacterial or parasitic infections^[35,36]. In Western countries, the infection rate of *H. pylori* is reported to be lower in patients with EoE^[33,37], and in the Asian EoE patients, eosinophilic

gastrointestinal diseases were reported to be infrequently accompanied by *H. pylori* infection^[38,39]. The infection rate observed in the present review also suggests a lower rate of *H. pylori* infection in Asian EoE patients than in the general Asian population.

For accurate diagnosis of EoE, a biopsy performed *via* upper gastrointestinal endoscopy is absolutely necessary. The presence of characteristic symptoms and endoscopic abnormalities is important for determining whether biopsy specimens should be collected. Dysphagia, the most frequently reported symptom of EoE in both Asian and Western countries, was found in nearly half of the patients reported in the studies covered by this review. Alternatively, food impaction was reported in less than 5% of Asian EoE cases, and this value was lower than that in Western countries^[40,41]. Endoscopy revealed longitudinal furrows in half of the Asian patients; thus, longitudinal furrows were the most frequently observed endoscopic abnormality in both Asian and Western EoE patients^[42-44]. As in Western studies, more than 80% of the Asian EoE patients showed endoscopic abnormalities characteristic of EoE, including longitudinal furrows, plaques, and concentric rings. These findings clearly indicate that Western and Asian EoE patients share similar symptoms and endoscopic abnormalities. This information is important for the accurate diagnosis of EoE. However, in Asian patients, fixed concentric rings/stenosis were not frequently found, although transient concentric rings were reported^[12,19,27]. The rarity of fixed concentric rings in Asian EoE patients is reasonable given the observation that food impaction is a rare symptom reported by Asian patients with EoE. The low grade of inflammation and the early stage of EoE disease at the time of diagnosis in Asian patients may be responsible for these differences in the clinical characteristics of EoE between Asian and Western patients.

EoE can be divided into two types, EoE and PPI-REE, based on the response of the disease to PPI administration. When administration of a PPI results in the resolution of EoE together with endoscopic abnormalities and symptoms, the appropriate diagnosis is PPI-REE^[1,2]. Alternatively, when a response to a PPI is not observed, the patient should be diagnosed with EoE according to the consensus of the published recommendations^[1,2]. However, some investigators have questioned the appropriateness of this classification. PPI-REE and EoE do not differ in regards to their clinical, endoscopic, or histological characteristics^[45-47], and the messenger RNA expression profile in the esophageal mucosa of PPI-REE and EoE cases has been reported to be nearly identical^[48]. In addition, PPIs have recently been shown to suppress Th2-type inflammatory responses, which are important for the development of EoE^[49,50]. Together, these findings suggest the limited importance and difficulty of PPI responsiveness in the classification of EoE. As a result, some investigators included PPI-

responsive EoE cases in their study population, whereas others did not. Seven studies covered by our review classified their study populations into PPI-REE and PPI-resistant EoE cases, and 23 (38%) of the 61 patients analyzed in those 7 reports exhibited PPI responsiveness. Although the percentage of PPI-REE cases reported by various studies differs remarkably in Western countries, 38% of the Asian cases were responsive to PPI administration, and this finding was generally similar to the results reported in Western countries^[46,51,52]. Additionally, PPI-resistant EoE patients in Asian countries were reported to be successfully treated *via* administration of glucocorticoid or dietary therapies, as has been reported in Western countries.

In summary, patients with EoE in Asian countries share similar clinical, endoscopic, and histopathological characteristics to those reported in Western countries, although the prevalence of EoE is lower in Asia. One-third of the Asian EoE patients responded favorably to PPI administration, whereas the others showed a good response to glucocorticoid or dietary therapy; these results were identical to those reported in Western countries. We conclude that EoE patients in Asian countries exhibit similar characteristics to those in Western countries.

COMMENTS

Background

The prevalence of eosinophilic esophagitis (EoE), a disease that is primarily caused by food allergies, is rapidly increasing in Western countries. EoE decreases health-related quality of life by causing dysphagia. The prevalence of EoE was reported to be approximately 50 per 100,000 individuals in the USA. However, the prevalence, the incidence, and the clinical characteristics of Asian patients with EoE have not been thoroughly investigated.

Research frontiers

Based on twin studies, the role of genetic factors in the development of EoE is approximately 20%. Therefore, with the westernization of social environments in Asian countries, EoE is expected to increase in a manner similar to that in Western countries. Accordingly, the prevalence and the clinical characteristics of Asian EoE patients need to be summarized and compared with those of Western EoE patients.

Innovations and breakthroughs

We have conducted a systematic literature search for studies on Asian patients with EoE. More than 200 such patients were found in the literature. The prevalence of EoE in Asian countries is lower than that reported in Western countries. The clinical characteristics of EoE are similar between Asian and Western countries, and common pathogenetic mechanisms are suggested. Possibly because of the lower grade of inflammation or the early stage of EoE at the time of diagnosis in Asian patients, endoscopic abnormalities and symptoms associated with EoE were less frequently observed in Asian patients than in Western patients.

Applications

The results of this study suggest that information concerning Western patients with EoE can be applied to Asian patients with EoE and that similar treatment strategies used in Western patients can be administered to Asian patients.

Terminology

The eosinophil is a type of leukocyte that increases and accumulates in allergic diseases. These cells, together with other inflammatory cells, cause inflammation in the esophageal mucosa, resulting in unpleasant symptoms. Dysphagia, or difficulty in swallowing, is the symptom most frequently reported by patients with EoE. Dysphagia significantly decreases patient quality of life.

Peer-review

Endoscopy examination is more popular in Asian countries, however, the

diagnosis of EoE is rare than that in Western countries. The authors reviewed the clinical characteristics of Asian EoE patients, which is helpful for the understanding of this disease in the East.

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The Number and Distribution of Eosinophils in the Adult Human Gastrointestinal Tract

A Study and Comparison of Racial and Environmental Factors

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Abstract: There are surprisingly limited data regarding normal counts or distribution of eosinophils in the gastrointestinal tract, despite the increasing incidence of eosinophilic gastrointestinal tract diseases. Moreover, there are no published reports on the eosinophil number throughout the gastrointestinal tract of adults or Asian populations, or those investigating the effect of race on eosinophil count. First, in our study, the number of eosinophils from each portion of the gastrointestinal mucosa was quantified on biopsy slides from a Japanese adult population (132 samples). Next, the surgical resections from Japanese (110 samples), Japanese Americans (64), and Caucasians (57) were used to investigate the racial and environmental effects. Our results with the Japanese biopsy samples showed a significant increase in the number of eosinophils from the esophagus to the right colon (mean \pm SD/mm²: 0.07 \pm 0.43 for the esophagus, 12.18 \pm 11.39 for the stomach, and 36.59 \pm 15.50 for the right colon), compared with a decrease in the left colon (8.53 \pm 7.83). Investigation using surgical samples showed that the distribution patterns in the gastrointestinal tract were very similar among the 3 ethnic groups, and there were no significant differences in the number of eosinophils among these groups, except in the esophageal epithelium. This study is the first report on the normal numbers and distribution of eosinophils throughout the gastrointestinal tract not only of an Asian population but also of adults. Our data suggest that a cutoff value for eosinophil counts, when rendering a diagnosis of eosinophilic gastrointestinal tract disease, should be individualized to the different biopsy sites. Interestingly, race and environmental factors did not seem to have a significant effect on eosinophil densities and distributions.

Key Words: normal, eosinophil, gastrointestinal tract, race

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The number of patients with allergic diseases such as asthma and atopic dermatitis has been increasing with improvement of environmental hygiene and sanitation. Along with this increase, patients suffering from digestive diseases associated with significant eosinophilic infiltration (ie, eosinophilic esophagitis and eosinophilic gastroenteritis) have also been reported to be increasing in number.^{1,2} To render a correct diagnosis in these patients, it is important to discern whether eosinophils are pathologically infiltrating the gastrointestinal tract mucosa. However, there are relatively little published data (5 reports^{3–7}) in reference to normal eosinophil counts or normal distribution of eosinophils in the gastrointestinal tract, and 3 of these 5 reports were focused only on children in Western countries. No report has investigated the normal distribution of eosinophils from the esophagus to the rectum of adults. Thus, to definitively make a pathologic diagnosis of eosinophilic gastrointestinal tract disease of adults in Asia, it is essential to quantify and characterize the eosinophil content in the normal gastrointestinal tract mucosa of the Asian populace.

Our main purpose was to know the content and distribution of eosinophils throughout the normal gastrointestinal tract mucosa of Japanese (J) using adult biopsy specimens. In addition, to our knowledge, no studies have been published regarding the effect of race on the eosinophil content in the normal digestive tract mucosa. Thus, our second purpose was to compare the number and distribution of eosinophils in the Japanese population with those in Japanese Americans (JA) and Caucasians (W), using surgical specimens.

MATERIALS AND METHODS

Our study was conducted at Shimane University Hospital and the Queens Medical Center. The former is located in Izumo, Japan (latitude 35.37, longitude –227.25), whereas the latter is in Honolulu, Hawaii (latitude 21.31, longitude –157.86). The research was approved by the ethical committees of Shimane University Hospital (approved #: 1145) and Queens Medical Center (approved #: RA 2012 07).

Patients and Sample Collection

The databases of both institutes were searched to identify samples suitable for the present study. The Japanese patients were living in Shimane prefecture located in the western part of Japan, and the American patients were in the state of Hawaii. Normal mucosal biopsy samples of Japanese subjects were taken from gastrointestinal tract mucosa that was endoscopically normal and histologically showed neither neutrophilic nor significant lymphoplasmacytic infiltration. All were outpatients of Shimane University Hospital. Most came to the hospital for their annual medical checkup without prominent symptoms. As is customary in Japan, gastrointestinal biopsies were sometimes taken to histologically confirm the patients' normal condition. Some had diarrhea and were suspected to have microscopic colitis without significant endoscopic findings. None of the patients had allergic diseases and eosinophilia in the peripheral blood, nor were they taking any steroids, antiallergic, or immunosuppressive drugs. The database also showed no past history of allergic diseases. We were able to include 34 esophageal (age 49 to 88, M:F-10:8), 35 gastric (age 25 to 90, M:F-16:15), 23 duodenal (age 37 to 88, M:F-9:14), 15 ileal (age 23 to 72, M:F-5:6), and 25 large intestinal (age 23 to 74, M:F-4:7) biopsy samples in our study. The surgical samples from all 3 ethnic groups were taken from the surgical margins of esophago-gastrointestinal resections for carcinomas of various stages (Table 1). The sampled sites were ≥ 5 cm away from the cancers. These sites macroscopically appeared normal and histologically exhibited no significant inflammation or neoplastic lesions. In addition, the patients who underwent surgery neither had allergic disease nor took any of the medications described above. They also had no eosinophilia in the peripheral blood and had no past history of allergic diseases. The gastric mucosa from both biopsies and surgical resections was free of *Helicobacter pylori* organisms. The period of study was from 1997 to 2012 for the Japanese group and from 2002 to 2012 for the Japanese American and Caucasian groups in Hawaii. Over 2000 gastrointestinal biopsies are taken and submitted to the Department of Pathology at Shimane University Hospital annually, and around 300 gastrointestinal surgeries for cancers are performed a year both at Shimane University Hospital and The Queens Medical Center. Despite the large numbers of biopsies and surgeries, it was very difficult to collect samples suitable for the present study, because we had to exclude so many cases in which the mucosa appeared endoscopically or macroscopically normal. The samples taken from apparently normal mucosa often showed significant lymphoplasmacytic infiltration, especially in surgical cases. This difficulty in sample collection accounts for small numbers and sex differences in the 3 groups.

Eosinophil Count

In this study, we microscopically examined normal gastrointestinal tract mucosa, including esophagus, stomach, and small and large intestines on hematoxylin

and eosin-stained slides. Microscopes used were Olympus BX50 for Japanese samples and Olympus BH2 for Japanese American and Caucasian samples. A high-power field (HPF) included an area of 0.237 mm^2 with Olympus BX50 and 0.196 mm^2 with Olympus BH2.

First, we attempted to clarify the numbers and distribution of eosinophils in each portion of the gastrointestinal tract using Japanese biopsy samples. Second, the comparison among the 3 ethnic groups was performed using surgical specimens, because normal biopsy samples from Japanese American and Caucasian groups were not readily available in Hawaii. Almost all of the esophageal biopsy specimens were composed only of stratified squamous epithelium, so that we were unable to evaluate the eosinophil numbers in the lamina propria adequately. However, an eosinophil count could be performed in the epithelium and the lamina propria separately and sufficiently when the surgical specimens were examined. Only the interfoveolar or intercryptal spaces of the mucosa were examined in the stomach and intestines. The areas around lymphoid follicles were excluded. Our cases showed no eosinophilic infiltration into the foveolar or cryptal epithelium. The average number of infiltrating eosinophils per HPF was calculated after counting them in 5 and 10 randomly selected HPFs for the biopsies and surgical specimens, respectively. The density of eosinophils was reported in the number of eosinophils/ mm^2 .

Statistical Analysis

Because the data were all nonparametric, the Mann-Whitney test was carried out for statistical analysis using SPSS software (version 17, Chicago, IL). A P value < 0.05 was considered to be statistically significant. The Bonferroni correction was used for comparisons among the 3 ethnic groups.

RESULTS

The representative histologic features of biopsy specimens taken from each segment of the gastrointestinal tract are shown in Figure 1. The eosinophil density varied greatly depending on the fields selected even within 1 biopsy slide, a finding consistent with that of Odze et al.⁸

Number and Distribution of Eosinophils in Biopsy Samples From Japanese Patients

Table 2 shows the statistical data obtained from examination of biopsies from each portion of the gastrointestinal tract of Japanese patients. As the sample number was relatively small, the gastric biopsies were not classified into fundus, body, or antrum, neither were the duodenal biopsies into the first through the fourth portions. Regarding the ileal mucosa, samples from only the terminal portion were available. The large intestine is often divided into right and left side anatomically; however, in a retrospective study like this report, it was not possible to clearly discern the exact location of the biopsy site of the transverse colon samples. For convenience, we divided the large intestine into 2 groups: cecum (C), ascending colon (A), and transverse colon (T) as right group (C/A/T) and descending colon (D), sigmoid

TABLE 1. Japanese (J), Japanese American (JA), and Caucasian (W) Samples (Surgical Samples)

	J			JA			W		
	Age (Range [Mean])	Sex	N	Age (Range [mean])	Sex	N	Age (Range [mean])	Sex	N
Esophagus	49-87 (70.5)	M:F = 29:4	33	53-89 (70.2)	M:F = 13:3	16	47-86 (67.4)	M:F = 8:2	10
Stomach	49-85 (70.5)	M:F = 11:5	16	34-93 (71.8)	M:F = 6:9	15	52-89 (68.5)	M:F = 11:1	10
Ileum (terminal)	55-93 (78.9)	M:F = 6:11	17	40-95 (72.2)	M:F = 6:13	19	46-87 (67.5)	M:F = 14:6	20
Large intestine (C/A/T)	55-97 (76.1)	M:F = 2:12	14	44-94 (70.2)	M:F = 2:4	6	45-79 (64.0)	M:F = 4:2	6
Large intestine (D/S/R)	40-90 (72.4)	M:F = 15:15	30	38-86 (68.1)	M:F = 5:3	8	48-90 (66.2)	M:F = 6:5	11

colon (S), and rectum (R) as left group (D/S/R). The mean eosinophil densities \pm SD of the esophagus, stomach, duodenum, terminal ileum, C/A/T, and D/S/R were $0.07 \pm 0.43/\text{mm}^2$ (range 0.00 to $2.52/\text{mm}^2$), $12.18 \pm 11.39/\text{mm}^2$ (range 0.00 to $39.64/\text{mm}^2$), $33.51 \pm 12.88/\text{mm}^2$ (range 12.64 to $56.44/\text{mm}^2$), $42.18 \pm 35.28/\text{mm}^2$ (range 10.95 to $119.63/\text{mm}^2$), $36.59 \pm 15.50/\text{mm}^2$ (range 16.85 to $56.45/\text{mm}^2$), and $8.53 \pm 7.83/\text{mm}^2$ (range 0.00 to $24.43/\text{mm}^2$), respectively. Figure 2 is the Box-and-Whisker plot to clearly show the data of Table 2. It reveals a statistically significant increase in the number of eosinophils from the esophagus to the duodenum. There were no significant differences in eosinophil counts among the duodenum, terminal ileum, and the C/A/T of the large intestine, but the number was significantly decreased in the D/S/R of the large intestine. The eosinophil counts varied considerably depending on the segment of gastrointestinal tract examined.

Effect of Race and Environmental Factors

Surgical gastrointestinal tract specimens were collected from Japanese, Japanese American, and Caucasian patients as described above. Because endoscopically normal parts of the gastrointestinal tract are rarely taken for histologic assessment at the Queens Medical Center, it was difficult to draw normal biopsy samples from their pathology database. Therefore, international ethnic comparisons were performed using surgical specimens including esophageal epithelium, esophageal lamina propria, gastric mucosa, terminal ileal mucosa, and C/A/T and D/S/R mucosa of the large intestine. Table 3 shows the data of the international comparisons. The paired data revealed that the number of eosinophils in the intraepithelial layer of the esophagus of Japanese patients was significantly higher than those of Japanese American (JA), Caucasian patients (W), and JA + W patients, when the Mann-Whitney test was used, although the difference between J and W became marginally significant after the Bonferroni correction ($P = 0.064$). There were no significant differences in other segments of the gastrointestinal tract among the 3 ethnic groups. Figure 3 shows the distribution patterns of eosinophils of all 3 ethnic groups with the statistical results. They were quite similar to one another with the terminal ileum and/or C/A/T of the large intestine showing the highest concentration of eosinophils for all 3 groups. The eosinophil content varied significantly depending on the site examined, just as was seen in the Japanese biopsy samples.

DISCUSSION

Eosinophil-associated gastrointestinal tract diseases including eosinophilic esophagitis and eosinophilic gastroenteritis have been prevalent mainly in Western countries.^{1,2,9,10} These eosinophilic gastrointestinal tract diseases, along with other allergic diseases such as atopic dermatitis and asthma, have also been on the rise in Asian countries.¹¹⁻¹⁴ Moreover, the number of adult patients has recently been increasing.^{15,16} Pathologic examination plays an important role in making a definitive diagnosis of eosinophilic esophagitis and eosinophilic gastroenteritis, and pathologists must take into account the normal number and distribution of eosinophils in gastrointestinal tract mucosa, when examining histologic specimens from patients with suspected eosinophilic gastrointestinal tract diseases. In addition, pathologists occasionally encounter biopsy specimens from the gastrointestinal tract with seemingly increased number of eosinophils without any other clinical indications of eosinophilic gastrointestinal tract diseases. However, in spite of the importance of pathologic examination, there is only limited information regarding the normal eosinophil count or normal distribution of eosinophils in gastrointestinal tract mucosa,³⁻⁷ rendering morphologic diagnosis of eosinophilic gastrointestinal tract diseases quite subjective. Lowichik and Weinberg³ and DeBrosse et al⁴ investigated the number of eosinophils throughout the gastrointestinal tract, but their reports were focused only on pediatric cases. Saad⁶ reported only on pediatric colon cases. Polydorides et al⁵ and Lwin et al⁷ examined the normal biopsy samples from adults, but their cases were colon and gastric biopsies, respectively. No report has investigated the number of eosinophils throughout the gastrointestinal tract of adults. Furthermore, the studies described above were all from Western countries. There has been no report on the number and distribution of the gastrointestinal tract of an Asian population. To diagnose patients as having eosinophilic esophagitis or eosinophilic gastroenteritis conclusively in Asian countries, it is imperative to know the eosinophil content and distribution in the normal gastrointestinal tract mucosa of Asians. Furthermore, no data have been published in reference to the effect of race and environmental factors on the eosinophil content in the normal gastrointestinal tract mucosa.

In the present study, we first evaluated the content and distribution of eosinophils using Japanese biopsy samples. When the ranges of the average number of each portion of gastrointestinal tract were calculated as the

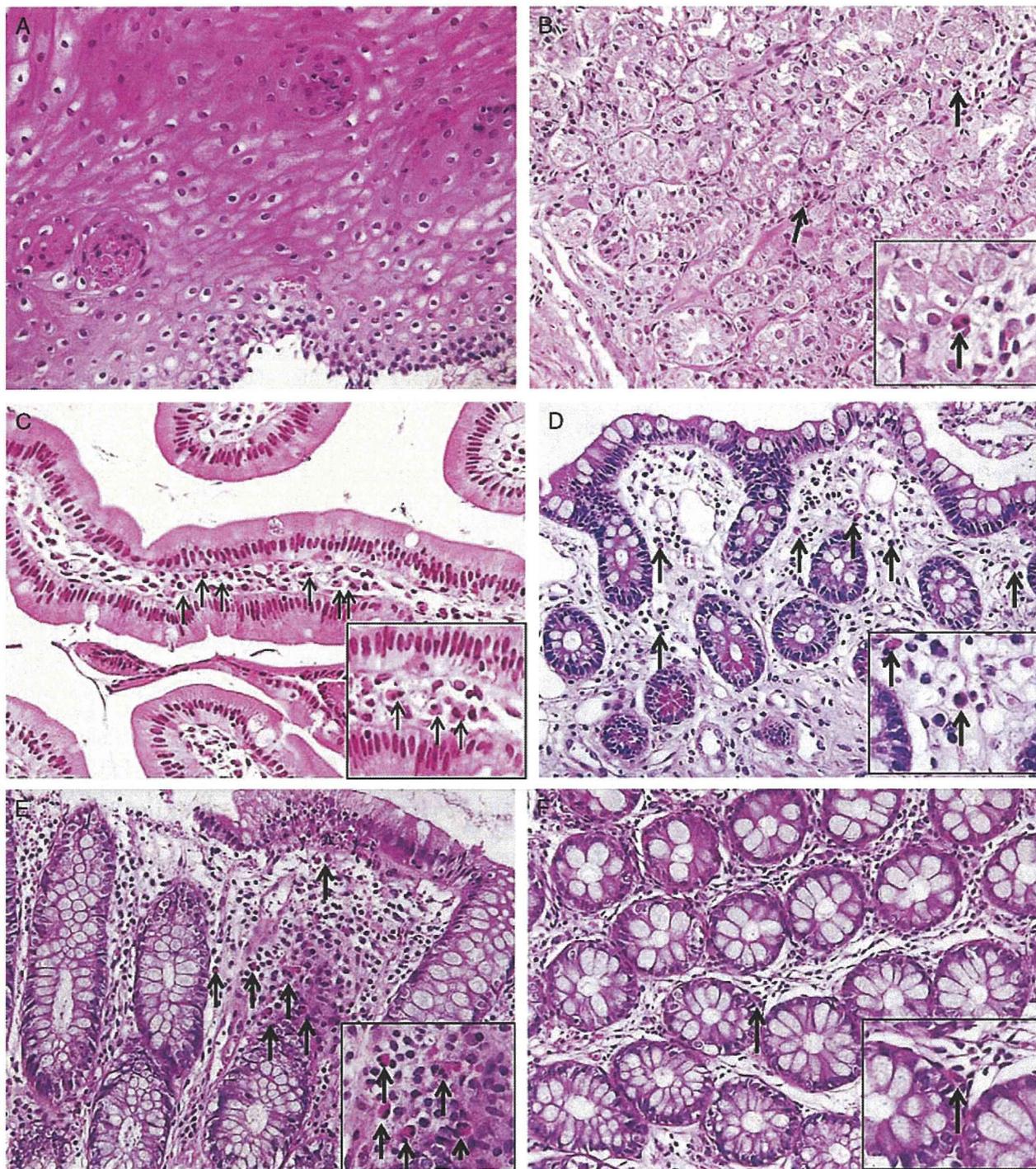


FIGURE 1. Representative histologic features of biopsy samples (hematoxylin and eosin). A, Esophageal epithelium. B, Gastric mucosa. C, Duodenal mucosa. D, Ileal mucosa. E, Ascending colon mucosa. F, Rectal mucosa. The arrows indicate some of the eosinophils present in the lamina propria. Insets of B through F are high-power images clearly illustrating eosinophils.

number/HPF with Olympus BX50, they were 0.00 to 0.60 for the esophagus, 0.00 to 9.39 for the stomach, 3.00 to 13.40 for the duodenum, 2.60 to 28.40 for the terminal ileum, 3.99 to 13.40 for the C/A/T of the large intestine, and 0.00 to 5.80 for the D/S/R. As expected, the number

of eosinophils detected in the esophageal biopsy specimens was very low, although we could not adequately assess the subepithelial layer with these sub-optimal biopsy samples. The highest detected eosinophil density ($2.52/\text{mm}^2$) could be correlated with an eosinophil

TABLE 2. Eosinophil Count in Japanese Biopsy Samples (Number/mm²)

	Mean	Median	SD	Variance	Range
Esophagus	0.07	0.00	0.43	0.19	0.00-2.52
Stomach	12.18	7.58	11.39	129.3	0.00-39.60
Duodenum	33.51	35.38	12.83	164.66	12.64-56.44
Ileum (terminal)	42.18	29.49	35.28	1244.63	10.95-119.63
Large intestine (C/A/T)	36.59	43.81	15.50	240.33	16.85-56.45
Large intestine (D/S/R)	8.53	6.32	7.83	61.33	0.00-24.43

count of 0.60/HPF with the use of Olympus BX50. It was accordingly confirmed that virtually no eosinophils were present in the normal esophageal epithelium, a finding in line with what we see in our daily pathology practice. The other highest average eosinophil densities of each segment correlated to 9.39/HPF, 13.38/HPF, 28.35/HPF, 13.38/HPF, and 5.79/HPF, respectively. The number of eosinophils significantly increased from the esophagus to the duodenum but it decreased in the D/S/R of the large intestine. This pattern of distribution is similar to the pediatric cases reported previously.^{3,4} However, Saad⁶ reported a gradual decrease in the number of eosinophils in the lamina propria from the cecum to the descending colon with another peak in the rectosigmoid. The cause of the difference in distribution pattern between our study and Saad's is unknown. As for adult normal colon, Polydorides et al⁵ reported that lamina propria eosinophils were, on average, 3 times more numerous in the ascending compared with the descending colon. The result reported by Lwin et al⁷ with their gastric biopsy cases was quite similar to ours in the present study.⁷ Regardless, we believe that a cutoff value for eosinophil counts, which is thought to be the most important histologic criterion when rendering a diagnosis of eosinophilic gastrointestinal tract diseases, should be individualized to the different biopsy sites. The number 15 to 20 eosinophils/HPF is described often in the current textbooks^{17,18} and used in most of the reports on eosinophilic gastrointestinal diseases as a cutoff value.¹⁹⁻²² However, we

consider that it may not be applied uniformly to all the segments of the gastrointestinal tract. Especially, in the terminal ileum and right side of the colon (C/A/T in the present study), the eosinophil count was often observed to be >20/HPF. In fact, the highest average eosinophil count was noted to be 28.60/HPF in the terminal ileum.

One might argue that the use of surgical resection specimens for carcinoma complicates the assessment of the normal number of eosinophils. We agree that surgical specimens are less suitable for elucidating accurate number of eosinophils than biopsy specimens, but we believe they can be used for international comparison as long as the sample collection method is strictly the same in each ethnic group. Our statistical data revealed a significant difference in eosinophil content in the esophageal intraepithelial layer at least between Japan and Hawaii, which might indicate that the racial or environmental factor has an effect on the eosinophil content as far as the esophagus is concerned. However, as described above, the study of Japanese biopsy samples detected very few eosinophils in the esophageal epithelium, with the highest average count of 2.52/mm² (0.60/HPF). Even the Japanese surgical samples showed a highest average count of only 7.16/mm² (1.70/HPF). As the eosinophil counts were so low, the statistical differences in the esophageal epithelium among the 3 groups might not be practically important when counting eosinophils. There were no significant differences in eosinophil content in the other portions of gastrointestinal tract mucosa among the 3 groups (J, JA, and W). Furthermore, the distribution patterns of eosinophils throughout the gastrointestinal tract mucosa were strikingly similar among the 3 ethnic groups. Therefore, the international comparison in the present study seems to indicate that race and environmental factors had only a little effect on the eosinophil concentration in the gastrointestinal tract mucosa, contrary to our expectation that there would be distinct statistical differences. Geographic variations in eosinophil concentration in normal colonic mucosa were studied by Pascal et al²³ in 1997. According to their study, the mean number of eosinophils was significantly higher in the southern compared with the northern United States. Their result is seemingly opposite from our study of eosinophil content in the colonic mucosa. However, as we just compared the eosinophil concentration of samples from Japan with those from Hawaii, it is possible that there is a difference between the 2 studies. Seasonal variation was not taken into account in the present study. However, interestingly, Polydorides et al⁵ found that the relationship between colonic eosinophilia and seasonal allergen exposure was not significant, although mucosal eosinophils were slightly more numerous in samples obtained in April and May. Furthermore, Sorser et al²⁴ reported that seasons did not affect the onset of symptoms of eosinophilic esophagitis in children and adolescents. There has been no literature investigating the effect of race on eosinophil concentration in gastrointestinal tract mucosa. However, further comparisons need to be undertaken among various ethnic groups, geographic areas, and seasons.

In summary, we have elucidated the number of eosinophils in the mucosa throughout the gastrointestinal

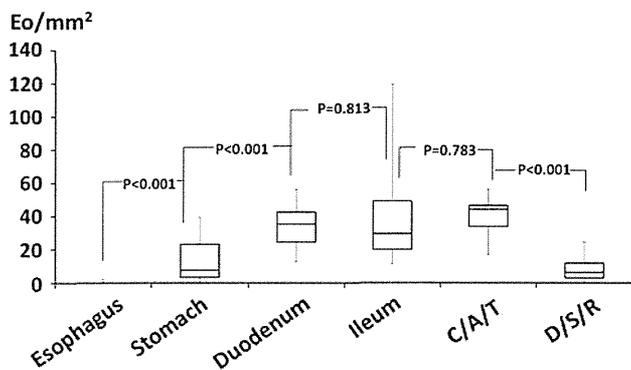


FIGURE 2. Eosinophil levels in gastrointestinal segments (Japanese, biopsy samples).

TABLE 3. Effect of Race and Environmental Factors on Eosinophil Number in Gastrointestinal Tract (Number/mm²)

	Mean ± SD (Range)				P			
	J	JA	W	JA+W	J Vs. JA	J Vs. W	JA Vs. W	J Vs. JA+W
Esophagus (IE)	0.82 ± 1.42 (0.00-7.16)	0.03 ± 0.13 (0.00-0.51)	0.36 ± 1.13 (0.00-3.7)	0.16 ± 0.70 (0.00-3.57)	0.001	0.028	0.856	< 0.001
Esophagus (SE)	5.63 ± 5.63 (0.84-23.59)	4.39 ± 4.55 (0.00-13.76)	4.48 ± 5.82 (0.00-18.34)	4.43 ± 4.96 (0.00-18.34)	0.442	0.286	0.737	0.258
Stomach	22.71 ± 16.81 (1.87-64.87)	36.35 ± 17.40 (7.13-91.21)	23.95 ± 26.68 (1.02-75.92)	31.39 ± 27.27 (1.02-91.21)	0.202	0.517	0.122	0.606
Ileum	97.05 ± 52.32 (24.01-203.88)	78.95 ± 41.14 (12.23-142.17)	70.04 ± 42.96 (0.51-178.34)	74.38 ± 41.77 (0.51-178.34)	0.379	0.141	0.310	0.606
Large intestine (C/A/T)	79.46 ± 47.03 (16.85-163.86)	73.12 ± 33.14 (19.87-109.55)	48.15 ± 43.39 (1.02-102.93)	60.6 ± 39.05 (1.02-109.55)	1.000	0.207	0.240	0.432
Large intestine (D/S/R)	38.59 ± 31.36 (2.53-106.99)	24.33 ± 20.78 (1.02-54.52)	30.67 ± 30.95 (0.00-93.76)	28.00 ± 26.66 (0.00-93.76)	0.297	0.315	0.840	0.182

IE indicates intraepithelial; SE, subepithelial (= lamina propria).

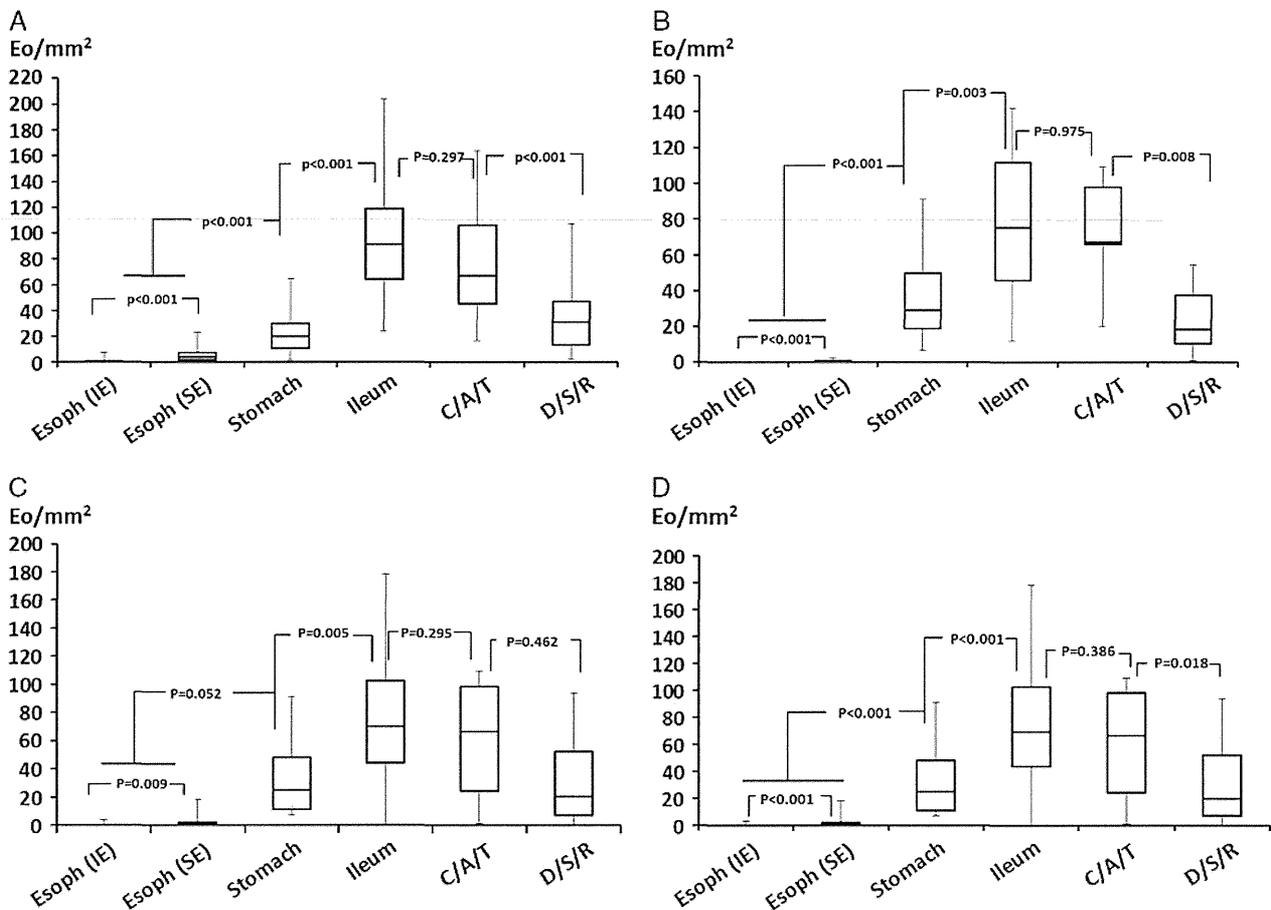


FIGURE 3. Eosinophil levels in gastrointestinal segments of the 3 ethnic groups (surgical samples). A, Japanese. B, Japanese American. C, Caucasian. D, Japanese American+Caucasian. IE indicates intraepithelial; SE, subepithelial (= lamina propria).

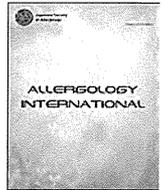
tract in a Japanese adult population. This is the first report of gastrointestinal tract eosinophil concentration and distribution in an Asian population. We believe that the histologic diagnosis of eosinophilic gastrointestinal tract diseases should be made on the basis of an individualized normal range of resident eosinophils. Our data suggest that race and environmental factors have only a little effect on eosinophil content at least between Japan and Hawaii, although the issue remains to be further clarified by additional investigation.

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Letter to the Editor

Proton pump inhibitor treatment decreased duodenal and esophageal eosinophilia in a case of eosinophilic gastroenteritis



Dear Editor

Primary eosinophilic gastrointestinal disorders (EGIDs), including eosinophilic esophagitis (EoE) and eosinophilic gastroenteritis (EGE), exclusively affect the gastrointestinal tract with eosinophil-predominant inflammation, where gastrointestinal eosinophilia secondary to other diseases, such as drug-induced and parasitic disorders, have been excluded.¹ In addition, EoE occasionally occurs secondary to EGE.

As recently suggested in U.S. guidelines for EoE,^{2,3} when EoE suspected by clinical and pathological findings responds well to proton-pump inhibitors (PPIs), it is distinguished from typical EoE as a newly recognized entity known as PPI-responsive esophageal eosinophilia (EE) (PPI-REE). Therefore, PPI trials using high-dose PPIs are recommended as a first-line therapy or diagnostic tool to distinguish PPI-REE from EoE. The effect of PPIs for gastrointestinal eosinophilia, except for PPI-REE, remain unknown. Here, we report a case of EGE associated with duodenal and esophageal eosinophilia successfully treated with a PPI.

Case report

A 2-year and 7-month-old girl underwent upper gastrointestinal endoscopic examination at our hospital for a follow-up. She had been diagnosed with EGID associated with duodenal eosinophil infiltration at 11 months of age.⁴ Elemental diet (ED) caused rapid weight gain and improved tracheal aspiration and esophageal clearance, but duodenal eosinophil infiltration persisted. The exacerbation of symptoms was not observed, and the ED was replaced with enteral formula, although she required the tubing of enteral formula because of difficulty in or reluctance to oral intake.

On upper gastrointestinal endoscopic examination, biopsies showed EE that had not been previously detected and persistent duodenal eosinophil infiltration with 106 eosinophils/high power field (HPF) and 72 eosinophils/HPF, respectively (Fig. 1A, B, respectively). According to the U.S. guideline for EoE,^{2,3} a PPI trial using oral lansoprazole (up to 30 mg/day) was begun in a subsequent clinic visit to determine her response. After PPI-treatment initiation, the patient's appetite improved, and subsequently, her amount of oral food intake increased gradually. Five months after starting PPI treatment, tube feeding was discontinued, and reevaluation of upper endoscopy was concurrently performed for pathological evaluation after PPI treatment. Duodenal eosinophilia and EE detected in the prior examination had drastically improved

(Fig. 1C, D, respectively). Afterwards, she consumed sufficient amounts of a variety of foods. Eight months after terminating tube feeding, PPI was tapered and discontinued. At the time of reporting this case, she remains symptom-free with a regular diet and no PPI treatment.

Discussion

Although a recent report showed that PPI-REE possesses significant molecular overlap with EoE,⁵ it remains to be determined if PPI-REE represents a subtype of EoE, a gastroesophageal reflux disease-associated condition, or a unique entity. In addition, the possible mechanisms of PPI action in EE⁵ may be a direct anti-inflammatory effect via blockade of IL-4- and IL-13-stimulated secretion of eotaxin-3⁶ and healing of disrupted epithelium as well as acid suppression, which may shorten eosinophil viability by increasing pH. Indeed, this patient's pH monitoring at first admission was negative. Taken together, although EE secondary to EGE may be much different from the conditions described above, PPI appears to be a promising treatment for this condition. In the present case, during the initial treatment, ED did not lead to complete remission, whereas PPI completely improved both clinical and histological findings. More surprisingly, the duodenal as well as esophageal eosinophil infiltrations nearly disappeared. Duodenal eosinophilia in this patient had never been improved well before. This may suggest that PPI also blocks the activation of STAT6 directly by IL-4 and IL-13 in the duodenal epithelium, since this inhibitory effect is not specific for esophageal epithelium and may be observed in many other cell lines.⁷ Measurements of gastrointestinal cytokine levels (such as with the string test) and pH in peri-PPI trials may be also important in revealing mechanisms.

A PPI trial may be the only way to distinguish PPI-REE from EoE because of their clinical and histological similarity. Therefore, the long-term prognosis of PPI-REE could vary. PPI alone may not be sufficient to induce complete remission; combining PPI with prior ED treatment might be required. Additionally, there is a possibility that ED did not induce complete remission due to other inflammatory conditions, such as *Helicobacter pylori* infection, as well as allergy, although the patient's allergy status was unclear. In order to dissect these mechanisms, allergy tests, such as the allergen-specific lymphocyte stimulation test and pylorus infection test, should be performed if the patient's EGIDs recur.

Two major treatments for EGE are considered in most cases.¹ One is the use of corticosteroids such as prednisolone. Additionally, especially in children, dietary eliminations have often been chosen

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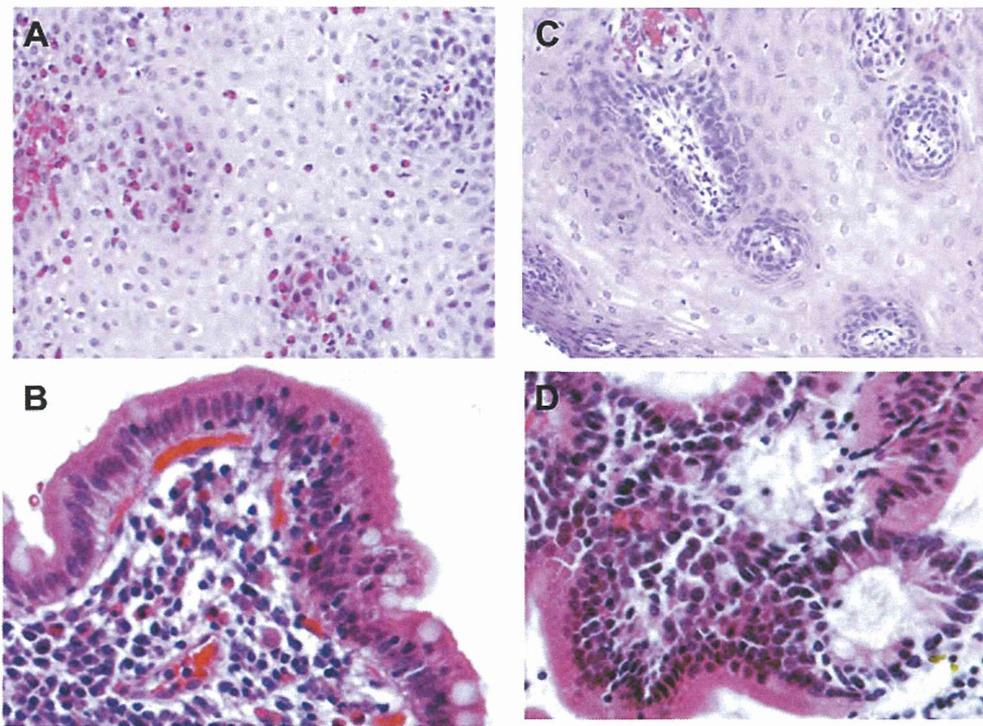


Fig. 1. Histological findings of esophagus and duodenum stained with H.E. before and after PPI-treatment. (A) Esophageal and (B) duodenal eosinophil infiltrations with 106 eosinophils/high power field (HPF) and 72 eosinophils/HPF respectively, are shown in pretreatment biopsies. (C) and (D) indicate esophagus with 1 eosinophil/HPF and duodenum with 3 eosinophils/HPF after PPI-treatment, respectively (Original optical magnifications: $\times 200$ in all figures).

for the treatment of EGE.⁸ When the possible causative foods are unknown or the effects of their elimination are restricted, amino acid-based EDs are used, often resulting in complete remission.¹ Therefore, ED was initially used, and the response was favorable in this case. However, difficulty in or reluctance to oral intake that may be associated with EGID⁴ and tissue eosinophilia remained, and our patient showed the first signs of improvement of them with PPI treatment, suggesting that PPI could promise a certain level of additive or synergistic effect with ED or dietary modifications.

Only nonspecific inflammation had been observed in her esophagus before. Usually, more than three esophageal biopsies are taken evenly from the proximal to distal esophagus in our hospital. Consequently, it is unlikely that we missed EE. EE can be a part of the findings of EGE and discovered during the course of EGE. Interestingly, there are previous reports of unusual cases of EGE in patients who had eosinophil infiltration, preferentially not in the epithelium but in the deep mucosal and submucosal layers of the esophagus⁹ or gastric muscularis,¹⁰ meaning that esophageal eosinophil infiltration can sometimes be primarily observed in places other than the superficial mucosa.

In conclusion, we describe a patient with an initial diagnosis of EGID with duodenal eosinophilic infiltration who developed EE during follow-up. PPI treatment used for the concurrent EE unexpectedly resulted in eradicating the duodenal eosinophilia as well as the EE, and overall symptomatic improvement was also observed. PPI treatment can be a promising additive approach even for EGE.

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Conflict of interest

The authors have no conflict of interest to declare.

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