

Clinical characteristics of Japanese patients with eosinophilic esophagitis and eosinophilic gastroenteritis

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Abstract

Background The clinical characteristics of Japanese patients with eosinophilic esophagitis (EoE) and eosinophilic gastroenteritis (EGE) have not been fully clarified. For understanding the pathogenesis as well as providing support for accurate diagnosis, precise information regarding clinical characteristics of these diseases is important.

Methods A questionnaire-based survey of EoE and EGE was conducted in 1,078 teaching hospitals. Clinical data of patients with confirmed EoE or EGE diagnosed from 2004 to 2009 were collected.

Result Clinical data from 26 patients with EoE and 144 patients with EGE were collected. The mean ages of patients in both groups were in the 40s. Those with EoE frequently complained of dysphagia and heartburn, and had

characteristic endoscopic features such as longitudinal furrows and multiple concentric rings in the esophagus, while only 34 % had peripheral eosinophilia. Patients with EGE frequently complained of abdominal pain and diarrhea, and approximately 80 % of them have peripheral eosinophilia. They did not have characteristic endoscopic features helpful for diagnosis. Computed tomography (CT) findings and the presence of peripheral eosinophilia were diagnostic for EGE. EGE patients with a small intestinal involvement showed the highest peripheral eosinophil counts. Glucocorticoid administration was the most widely used treatment for these diseases and its effect was favorable for at least induction of remission.

Conclusion EGE is more prevalent than EoE in Japan. Patients with EGE have abdominal pain and diarrhea, high peripheral eosinophil counts, and gastrointestinal wall thickening identifiable by CT findings, while EoE is characterized by dysphagia and characteristic endoscopic features.

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Introduction

Eosinophilic esophagitis (EoE) and eosinophilic gastroenteritis (EGE), which are included in eosinophilic gastrointestinal disorders (EGIDs), are rare pathological conditions characterized by dense infiltration of eosinophils in esophago-gastro-intestinal mucosa [1, 2]. Motor, digestive, and sensory functions of the involved alimentary tract are severely damaged by chronic inflammation, mainly caused by eosinophils. 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. Common pathological conditions including exaggerated Th2 response to environmental and food allergens are considered to have important roles in these conditions [3–5]. Partly because of changing environmental factors and food antigens, and partly because of lower exposure to microorganisms that change from Th2 dominant individuals to Th1 dominant ones, the prevalence of EoE is rapidly increasing, especially in western countries [6–9]. The clinical characteristics of EoE patients in western countries have been extensively investigated [5, 10, 11], whereas those of EGE have not been fully clarified. In Japan, the prevalence and clinical characteristics of EoE and EGE have yet to be investigated in a large cohort, though we previously reported the prevalence of EoE in a smaller study [12]. A nationwide survey of EoE and EGE is important not only for understanding prevalence rates, characteristics, and commonly used therapies, but also for revealing possible clinical differences between Japanese and western patients with EoE and EGE.

We conducted a nationwide survey of EoE and EGE, and analyzed their clinical characteristics. We found similarities and differences for these two diseases, which may be important not only for the diagnosis but also for understanding their pathogenesis.

Materials and methods

We sent questionnaires to 1,078 teaching hospitals who were rated as high quality by the Japanese Society of Gastroenterology in 2010. The questionnaire contained queries concerning the clinical characteristics of patients with EoE and EGE diagnosed in each hospital from 2004 to 2009. The items surveyed in the questionnaire included age, sex, symptoms, laboratory data, radiologic/ultrasonographic

examination findings, endoscopic examination findings, and treatments (Supplemental Figure).

Responses to the questionnaires were analyzed and evaluated by an independent analysis team (KF, NI, SI, SS). Cases with clinical characteristics that were appropriately described and had an appropriate diagnosis confirmed by histopathological findings were subjected to analysis. The diagnostic criteria employed were the same as those previously reported in the literatures [10, 13]. Proton pump inhibitor (PPI) responsive symptomatic patients with esophageal eosinophilic infiltration over 20 eosinophils/HPF (high power field) were also collected as EoE in this survey. The study protocol was approved by the ethics committee of Shimane University School of Medicine.

Statistical analyses were done using Stat View software. Chi-square tests and unpaired *t* tests were used as appropriate. When the data were not normally distributed, non-parametric tests were used. Values shown represent the mean \pm SE or the median and ranges. $p < 0.05$ was considered to be statistically significant.

Results

Basic clinical characteristics

Twenty-six patients with EoE and 144 with EGE were identified in the questionnaire-based survey. Thus, we concluded that the prevalence of EGE is approximately 5.5 times higher than that of EoE in Japan. The male/female ratio for EGE was 1.2:1, while that for EoE was 3.3:1 with male preponderance. Both diseases were frequently observed in middle aged persons, with younger patients more frequently found to have EGE (Table 1; Fig. 1).

In both EoE and EGE cases, approximately half of the patients had a history of allergic diseases. Bronchial asthma was the most frequently observed allergic condition and was found in 23.1 and 27.8 % of the patients with EoE and EGE, respectively. Atopic dermatitis, food allergy, and allergic rhinitis were also frequently observed (Table 1).

In 26 EoE cases, 4 patients showed symptomatic improvement after PPI administration. There was no difference in clinical characteristics between PPI responsive and non-responsive cases.

Symptoms

Patients with EoE complained of dysphagia, heartburn, and other esophageal symptoms such as chest discomfort, throat discomfort, and regurgitation. Dysphagia was the most frequently observed symptom in 46 % of the patients. In contrast to findings in western countries [10, 14, 15], none of the present patients had a history of food

Table 1 Clinical characteristics of surveyed patients with EoE and EGE

	EoE	EGE
<i>N</i>	26 (including 4 PPI responsive cases)	144
M/F	20/6	78/66 ^a
Age (years)	49 ± 3	46 ± 2
Presence of allergic disease (duplicate count)	50 %	46 %
Bronchial asthma	23.1 %	27.8 %
Atopic dermatitis	7.7 %	6.3 %
Food allergy	11.5 %	6.3 %
Allergic rhinitis	15.4 %	10.4 %
Symptoms (duplicate count)		
Dysphagia	46 %	–
Heartburn	8 %	–
Chest pain	–	15 %
Abdominal pain	–	53 %
Diarrhea	–	54 %
Others	50 %	42 %
GI wall thickening by CT	53 % (9 cases/17 investigated cases)	75 % (83 cases/111 investigated cases)
Endoscopic features (duplicates counted)		
Longitudinal furrows	35 %	–
White plaque	23 %	–
Concentric rings	19 %	–
Erythema	–	38 %
Edema	–	42 %
Erosion	–	43 %
Others	–	3 %
Normal	42 %	11 %
Involved GI tract (duplicates counted)		
Esophagus	100 %	9 %
Stomach	0 %	31 %
Small intestine	0 %	72 %
Colon	0 %	42 %
Ascites	0 %	56 % (48/85 investigated cases)

PPI proton pump inhibitor, EoE eosinophilic esophagitis, EGE eosinophilic gastroenteritis

^a Significantly different from EoE ($p < 0.05$)

impaction. All patients with EoE had some symptoms that suggested the presence of esophageal disease.

Patients with EGE frequently complained of abdominal pain, diarrhea, and chest pain. Abdominal colic pain with diarrhea was the most frequent complaint, and over 40 % of the EGE patients had this type of symptom complex. There were no age-related or sex-related differences in regard to the reported symptoms.

Laboratory findings

Peripheral leukocyte counts, peripheral eosinophil counts, and CRP were routinely measured when a diagnosis of EoE or EGE was made (Table 2). Among the patients with EoE, 23.1 % had an elevated leukocyte count greater than 9,000/ μ l (Fig. 2), while the median and range for peripheral leukocyte count were 6,830 (4,400–21,400)/ μ l. Eosinophilia was defined as a peripheral eosinophil count over 600/ μ l according to the previous publication [16]. An elevated peripheral eosinophil count greater than 600/ μ l was found in 34.6 % of the patients with EoE, and the median and range for eosinophil count were 446 (162–8,774)/ μ l. The median CRP level in patients with EoE was 0.1 mg/dl.

In patients with EGE, peripheral leukocytes and eosinophils counts and plasma CRP level were all higher as compared to EoE, with 49.3 % of the EGE patients showing an elevated leukocyte count greater than 9,000/ μ l [median and range for all EGE cases, 8,970 (3,100–97,800)/ μ l]. Peripheral eosinophil count was elevated in 80.6 % of patients with EGE. The CRP level was also elevated over 2.0 mg/dl in 17.4 % of the patients with EGE.

In patients with EGE, involved lesions were most frequently found in the small intestine followed by the colon. Nine percentages of patients with EGE had esophageal lesions as well. The median peripheral eosinophil count in patients with esophago-gastric, small intestinal and colonic lesions was 1,462/ μ l, 2,656/ μ l, and 616/ μ l, respectively. Patients with small intestinal involvement had a significantly higher peripheral eosinophil count (Table 3; Fig. 3).

Radiological examination findings

Seventeen of 26 patients with EoE were examined using CT, and over 50 % of those demonstrated thickened esophageal walls. CT examinations were also performed in 77 % of the patients with EGE, and thickened gut walls were seen in 75 % of those cases. In addition, ascites were detected in approximately 56 % of the investigated patients with EGE. Except thickened esophago-gastrointestinal walls, no specific morphological feature that could be helpful for the diagnosis was found in the description of the radiological findings on the questionnaires.

Endoscopic findings

Endoscopic examinations were performed for all of the reported cases. Esophageal mucosal longitudinal furrows (35 %), white plaque (23 %), and multiple concentric rings (19 %) were frequently observed characteristic endoscopic features of EoE, as has also been reported in western countries [17, 18] (Table 1).

Fig. 1 Age distribution of surveyed patients with EoE (a) and EGE (b). *Open columns* represent female patients and *hatched columns* represent male patients. In addition to the middle-aged patients, younger patients with EGE were frequently found

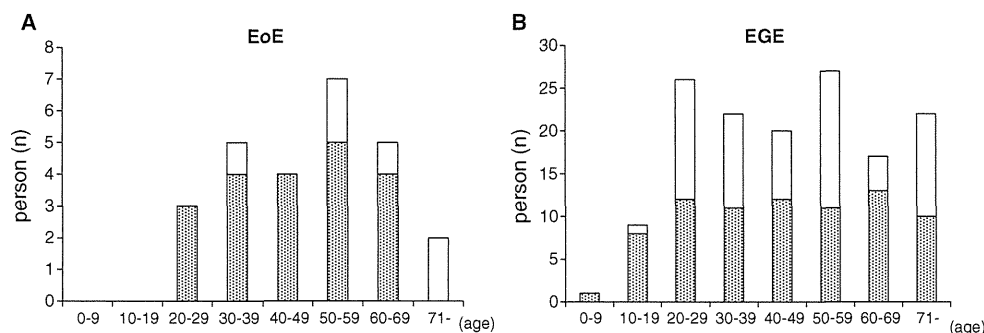


Table 2 Laboratory data from surveyed cases

	EoE	EGE
CRP	0.1 (0.03–2.9) mg/dl	0.29 (0.0–18.0) mg/dl ^a
WBC	6,830 (4,400–21,400)/μl	8,970 (3,100–97,800)/μl ^b
Eosinophils	446 (162–8,774)/μl	2,130 (3–58,860)/μl ^b

Medians and ranges in parenthesis

EoE eosinophilic esophagitis, *EGE* eosinophilic gastroenteritis

^a Significantly different from EoE ($p < 0.05$)

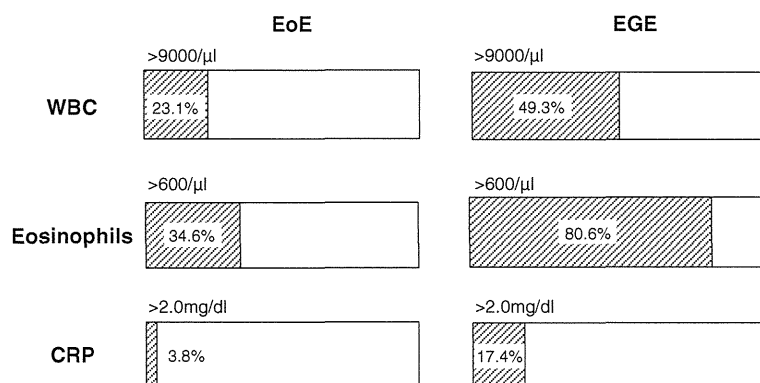
^b Significantly different from EoE ($p < 0.01$)

Over 95 % of the patients with EGE had endoscopic abnormalities found on the mucosal surface of involved alimentary tract. The most frequently observed mucosal lesions were edema, erosion, and erythema, though no specific characteristic endoscopic findings for EGE was found.

Treatments and response

Oral glucocorticoid administration was employed in two thirds of the EoE patients, and all except one responded favorably. Oral glucocorticoid therapy was also used for almost all of the patients with EGE, and the responses were favorable, at least in short-term observations. A variety of anti-allergic drugs such as montelukast, epinastine, and suplatast tosilate was given with and without combined administration of glucocorticoids, although their therapeutic effects were not confirmed to be effective.

Fig. 2 Percentage of patients with EoE or EGE who showed abnormally elevated peripheral leukocyte, and eosinophil count or CRP level. *Hatched columns* represent the patients with abnormal elevation of peripheral leukocytes, eosinophils, or CRP level



Discussion

In this report, the largest number of EGEs in the world literature and the largest number of EoEs in the Japanese literature were analyzed. This survey clarified the clinical characteristics of Japanese patients with EoE and EGE. Although they were similar to those reported in western countries [12, 19, 20], a remarkable difference was that the prevalence of EoE in Japan was lower than that of EGE.

The lower prevalence of EoE in Japan may be explained in part by the Japanese general practitioners' limited knowledge about EoE and also because of the difficulty in diagnosis, in addition to a true lower incidence of EoE in Japan [21]. Elevated CRP levels and peripheral leukocyte counts were found in fewer than 35 % of the analyzed cases of EoE. The finding of thickened esophageal walls detected by CT was similar to that reported in EoE patients from western countries [22–24]. Endoscopic findings in the present cases were also similar to western populations, with longitudinal furrows, white plaque, and multiple concentric rings frequently observed endoscopically as mucosal changes [18, 25, 26]. Importantly and similar to the western reports, 40 % of the surveyed patients had no esophageal mucosal lesions identified on endoscopic examinations [18]. The difference we found was older age of the Japanese patients with EoE as compared to western patients [18, 27, 28]. The similar characteristics of EoE between the present Japanese cases and those in western regions suggest

Table 3 Clinical and laboratory data from EGE cases classified by involved organs

	EGE		
	Esophagus/stomach	Small intestine	Large intestine
<i>N</i>	19	104	23
<i>M/F</i>	10/9	59/45	9/14
Age	48 ± 4	47 ± 2	45 ± 4
Presence of allergic disease	47 %	45 %	44 %
Symptoms (duplicates counted)			
Chest pain	26 %	14 %	4 %
Abdominal pain	21 %	56 % ^a	65 %
Diarrhea	16 %	59 % ^a	61 %
Others	58 %	41 %	30 %
CRP (mg/dl) median (range)	0.30 (0.0–9.2)	0.29 (0.0–13.5)	0.10 (0.0–18.0)
WBC (/μl) median (range)	7,740 (3,100–21,780)	10,415 (4,200–97,800) ^{a, b}	6,900 (3,620–19,700)
Eosinophils (/μl) median (range)	1462 (117–15,202)	2,656 (3–58,860) ^{a, b}	616 (90–13,790)

Esophagus/stomach group includes cases with esophagus and/or stomach lesions but without small intestinal lesions

Small intestine group includes cases with small intestinal lesions

Large intestine group includes cases with large intestinal lesions but without small intestinal lesions

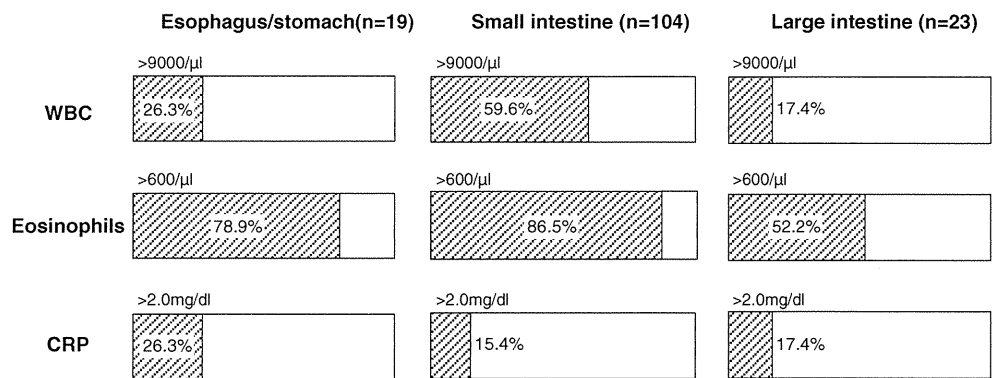
Two cases are included in both the esophagus/stomach and large intestine groups, as they had gastric and large intestinal lesions, but no small intestinal lesions

EGE eosinophilic gastroenteritis

^a Significantly different from esophagus/stomach group (*p* < 0.05)

^b Significantly different from large intestine group (*p* < 0.05)

Fig. 3 Percentage of EGE patients with different involved site of gastrointestinal tracts who showed abnormally elevated peripheral leukocyte and eosinophil counts or CRP level. *Hatched columns* represent the patients with abnormal elevation of peripheral leukocytes, eosinophils, or CRP level



a common pathogenesis of EoE among ethnically different populations.

In this survey, we analyzed 144 cases of EGE, making this the largest of its kind reported worldwide. The characteristics of the Japanese patients with EGE were similar to those reported from other Asian countries [29]. Patients with EGE had several clinical characteristics similar to those with EoE, although there were more abnormalities in the laboratory data than in EoE patients. The reason why the abnormalities of peripheral eosinophil count and CRP level were more prominent in EGE than in EoE cases is not clear. One possible reason is the larger volume of the

involved gastrointestinal tract in patients with EGE as compared to EoE. In addition, the specific involved lesion may be important for determining the peripheral eosinophil count and CRP level. In the present survey, the small intestine was the most frequently involved organ in patients with EGE, as also reported in western countries [13, 30]. The small intestine, which has abundant lymphatic tissues, is the most active alimentary tract participating in immune reactions [31]. Therefore, patients with small intestinal lesions may show stronger immunologic and inflammatory responses. Indeed, in patients without small intestinal involvement, the mean peripheral eosinophil count was less

than 9,000/ μ l, while in those with small intestinal lesions it was 14,209/ μ l (Table 3).

Approximately half of the surveyed patients with EoE had dysphagia, which may be caused by esophageal motor dysfunction or esophageal stenosis related to edema or fibrosis. Patients with EoE have been reported to have esophageal motor dysfunctions and decreased esophageal distensibility [32–35]. As for surveyed patients with EGE, more than 50 % complained of abdominal pain and/or diarrhea, as also noted in other surveys [16, 29, 36]. In patients with small intestinal and/or colonic involvement, abdominal pain and diarrhea were frequently observed, while in those with only esophago-gastric involvement, a minority reported abdominal pain or diarrhea.

For diagnosis of EoE, an endoscopic examination with a biopsy is considered to be useful, since affected patients frequently have characteristic endoscopic features such as longitudinal furrows and multiple concentric rings in the esophagus, which was clarified in the present survey and also reported in western populations [18]. Approximately 40 % of the present patients with EoE, however, had no characteristic endoscopic finding. Therefore, a biopsy is recommended for the evaluation of patients with PPI-resistant esophageal symptoms, even if they have no endoscopic abnormalities. Miller et al. [37] reported the good cost-effectiveness of this type of approach in the US. Since both the prevalence of EoE and cost of an endoscopic biopsy examination are lower in Japan, the cost-effectiveness of the diagnostic strategy with an endoscopic biopsy examination for PPI resistant patients should be re-examined in Japan.

In patients with EGE, an endoscopic examination can only detect non-specific mucosal lesions such as edema, erosion, and erythema. Therefore, the diagnostic value of an endoscopic examination is lower in EGE if an endoscopic biopsy is not performed. Unlike EoE, patients with EGE frequently have ascites and increased peripheral eosinophils. Therefore, for the diagnosis of EGE, a combination of laboratory tests and endoscopic/radiological image analysis is considered to be important. Of note, CT is especially useful, as over 70 % of the involved lesions were detected by such an examination in this survey.

For treatment of both EoE and EGE, systemic or topical glucocorticoid administration was employed as first-line treatment in nearly all the surveyed cases, as noted in the consensus recommendations [11]. The long-term effects of such treatment, especially after the initial induction treatment, have not been fully clarified, while the short-term remission induction effect was found to be adequate in our survey. Recently, the natural history of EGE was reported in a study of 43 patients, of whom 40 % experienced spontaneous disease resolution, while the clinical course was more complex and disease relapse was common despite the repeated glucocorticoid treatments in other

cases [38]. The long-term clinical courses of patients with EoE and EGE were not surveyed; thus, a future nationwide cohort study will be necessary to clarify the long-term clinical course in Japanese patients.

This study has several limitations especially in the study design. The questionnaire we sent has several descriptive questions in it. Therefore, the quality and quantity of the information collected strongly depend on the attending gastroenterologists. In addition, for the diagnosis of EoE and EGE, other diseases that may cause esophago-gastrointestinal eosinophil infiltration need to be ruled out. This diagnostic process also depends on the attending gastroenterologists. These uncertainties and the possible inhomogeneity of the diagnostic process may limit the value of this survey. Diagnosing EGE may have an additional difficulty. Because of the resident eosinophils present in normal gastrointestinal mucosa, the histological diagnosis of EGE is not easy without the defined cutoff value of infiltrating eosinophils. Therefore, based on the results of this survey, the establishment of diagnostic criteria containing the cutoff value of the number of tissue eosinophils especially for EGE is considered important. The third limitation of this survey is the lack of a maximum eosinophil infiltration number in different parts of the gastrointestinal tract of the patients with EGE. When the survey was conducted, the necessary maximum number of eosinophils infiltrating the gastrointestinal tract was not described in the diagnostic criteria. Therefore, in future studies, we need to investigate the number of infiltrating eosinophils and to compare it to the patients' clinical characteristics.

In summary, we surveyed the clinical characteristics of Japanese patients with EoE or EGE. EGE was more prevalent in Japan. EGE patients were typified by abdominal pain and diarrhea symptoms, high peripheral eosinophil counts, and gastrointestinal wall thickening, identifiable in CT findings. EoE was characterized by dysphasic symptoms and characteristic endoscopic features.

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Conflict of interest We have no COI with any commercial groups concerning the manuscript. We, the authors of this manuscript, indicate that we have no financial relationship to any commercial groups. We also state that we have full control of all primary data and that we agree to allow the journal to review our data if requested.

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