

Similarities and differences among eosinophilic esophagitis, proton-pump inhibitor-responsive esophageal eosinophilia, and reflux esophagitis: comparisons of clinical, endoscopic, and histopathological findings in Japanese patients

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Abstract

Background Esophageal eosinophilia is classified as either eosinophilic esophagitis (EoE) or proton-pump inhibitor-responsive esophageal eosinophilia (PPI-REE), depending on the response to PPI treatment. The aim of this study was to compare the clinical, endoscopic, and histopathological findings of EoE and PPI-REE in Japanese patients. In addition, the characteristics of these cases were compared with those of reflux esophagitis (RE) cases.

Methods Eleven patients diagnosed with EoE, 16 with PPI-REE, and 39 with RE, who were all consecutively examined from 2005 to 2015 at Shimane University Hospital, were enrolled. Clinical, endoscopic, and histopathological esophageal findings in these groups were retrospectively examined and compared.

Results The differences in the clinical characteristics of EoE and PPI-REE were not remarkable, though patients with EoE and PPI-REE were younger, presented a higher prevalence of allergic comorbidities, and complained of symptoms of dysphagia more frequently than those with RE. The only noteworthy differences between EoE and PPI-REE were more frequent reports of asthma (36.4 vs. 2.6 %) and food allergy (27.3 vs. 0 %) by patients with EoE ($P < 0.05$, $P < 0.05$, respectively). Endoscopic findings in patients with EoE and PPI-REE were similar, with the presence of esophageal erosions in a small percentage

of PPI-REE cases being the only difference. There were no histopathological differences between EoE and PPI-REE.

Conclusions Comparisons of clinical, endoscopic, and histopathological findings between EoE and PPI-REE showed that these two types have similar characteristics, though EoE patients showed a higher atopic background. Predicting PPI responsiveness in cases with esophageal eosinophilia is difficult and requires further investigation.

Keywords Allergy · Reflux esophagitis · Endoscopy · Eosinophile · Proton-pump inhibitor

Introduction

Esophageal mucosal eosinophile infiltration is a pathological condition caused by an allergic reaction to food or airborne allergens, with an increasing number of cases reported. This pathological condition shows dense infiltration of eosinophils and related chronic inflammation in epithelial layers of the esophageal mucosa [1]. Eosinophile-related chronic inflammation causes remodeling of esophageal submucosal layers and results in fibrous stricture of the esophagus over a long clinical course [2]. The intensity of eosinophile infiltration and inflammation has been investigated using biopsy samples obtained from various parts of the esophagus, which have revealed greater severity in the distal portion of the esophagus as compared to the proximal parts [3–5]. Although the mechanism responsible for stronger eosinophile-related inflammation in the distal esophagus has not been clarified, gastric acid reflux may have a role in the predominant eosinophile infiltration there [6–8].

To relieve esophageal symptoms and prevent future stricture, pharmacological intervention is the standard

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treatment strategy for esophageal eosinophile infiltration. The most commonly used first-line treatment option is administration of a proton-pump inhibitor (PPI) for at least 2 months, as that has been reported to relieve esophageal symptoms, endoscopic abnormalities, and eosinophile infiltration in approximately 50 % of treated cases [9, 10]. According to consensus recommendations reported in 2011, esophageal eosinophile infiltration that does not respond to PPI administration is termed eosinophilic esophagitis (EoE), while that showing a response is diagnosed as PPI-responsive esophageal eosinophilia (PPI-REE) [1]. As it is a pathogenetic factor for PPI-REE, gastroesophageal acid reflux may play a role similar to that seen in cases with reflux esophagitis (RE).

Several studies conducted in Western countries have found similarities in the clinical and histopathological characteristics of EoE and PPI-REE, and have suggested that it is difficult to predict the response to PPI administration in patients with esophageal eosinophilia [11–14]. The prevalence of EoE has been reported to be very low in Asian countries, and its pathogenesis as well as that of PPI-REE may be different in Asians, indicating the need for a different therapeutic strategy [15–18]. In the present study, clinical, endoscopic, and histopathological findings in cases of EoE, PPI-REE, and RE in Japan were analyzed and compared in order to find possible predictive factors for PPI responsiveness in Japanese patients.

Methods

Subjects

The records of all Japanese patients of Shimane University Hospital with esophageal eosinophile infiltration and RE diagnosed based on endoscopic and histological findings from January 2005 to December 2015 were initially analyzed in this retrospective study. Cases treated with drugs which may have influenced gastroesophageal function and modulated the immune system were excluded.

Twenty-seven cases of dense esophageal epithelial infiltration of eosinophils (greater than 15/high-power field, HPF, 400×) were found and enrolled for further analysis. Each was initially treated by administration of a PPI at a standard or higher dose for at least 2 months. Eleven did not respond to that administration (9 at the standard dose and 2 at a higher dose), as esophageal symptoms and dense eosinophile infiltration of over 15/HPF remained, and were diagnosed with EoE according to current guidelines [1, 19]. On the other hand, 16 patients responded to PPI treatment at the standard dose, with both symptoms and eosinophile infiltration disappearing within the 2-month administration period. The rate of PPI responsiveness was 59 % in this

study. Based on their PPI responsiveness, these 16 patients were diagnosed with PPI-REE.

Thirty-nine patients with RE were also enrolled. Biopsy specimens from esophageal mucosa obtained from areas near mucosal breaks confirmed by endoscopy were reviewed to determine eosinophile infiltration and epithelial damage for this study. All patients with RE were treated by administration of a PPI later and responded favorably, confirming that gastroesophageal acid reflux is a pathogenic factor for the disease.

As a result, a total of 66 patients were enrolled in this retrospective observational study. The study protocol was approved by the Ethical Committee of the School of Medicine of Shimane University.

Clinical, endoscopic, and histological findings

Clinical data including demographics (age, gender, height, weight), clinical presentation (dysphagia, heartburn, etc.), atopic background (bronchial asthma, atopic dermatitis, etc.), and peripheral blood test results were independently extracted from the medical records of the enrolled patients by two of the authors (N.I., Y.K.), and more than 99 % of the data extracted by each investigator matched the data extracted by the other investigator. For the nonmatching data, a consensus meeting was held to review the medical records together.

Images obtained with endoscopy—at least 40 for each patient—were separately reviewed by three of the authors (N.O., H.M., M.A.) and classified according to a standardized method. They were blinded in regard to the clinical diagnosis of each case. Mucosal breaks in patients with RE were graded according to the Los Angeles classification [20]. A hiatal hernia was diagnosed when longer than 2 cm. Atrophy of gastric mucosa was graded according to the Kimura–Takemoto classification [21]. For the closed type, a grade of C1–3 indicated milder gastric mucosal atrophy, while a grade of O1–3 for the open type indicated more severe gastric mucosal atrophy. Typical endoscopically identifiable mucosal lesions of EoE/PPI-REE, such as the presence of esophageal mucosal longitudinal furrows, multiple concentric rings, strictures, and white plaque, were evaluated according to the previous reports [3, 22, 23]. Mucosal redness was defined as mucosal erythema or reddening without erosion [24], while edema was defined as an absence of vascular markings corresponding to grade 2 (severe) in a recently reported endoscopic classification and grading system for EoE [25].

Histopathological findings of biopsy samples were reviewed by surgical pathologists (R.M., N.I., M.N.), each of whom is board certified for surgical pathology in Japan. They were blinded in regard to the clinical diagnosis of the patients. The maximal numbers of eosinophils,

lymphocytes, and neutrophils per HPF were determined [26–28]. In addition, the presence of epithelial basal cell hyperplasia, balloon cells, and dilated intercellular spaces in the middle epithelial layer (spongiosis) was evaluated.

Statistical analysis

Statistical comparisons between groups were made by ANOVA, followed by a Mann–Whitney *U* test. A chi-squared test was also used as appropriate. After identifying significant predictors by univariate analysis, multivariate logistic regression analysis was performed to evaluate independent predictors of EoE. *P* < 0.05 was considered to indicate a statistically significant difference. All values are shown as the mean ± SE.

Results

Clinical characteristics

The clinical characteristics of patients diagnosed with EoE, PPI-REE, and RE are shown in Table 1. Patients with EoE or PPI-REE were significantly younger than those with RE. Furthermore, over 90 % of the patients in those two groups were male, as compared to 62 % of the patients with RE. Values for height, body weight, and BMI were lower in patients with RE than in those with PPI-REE, whereas there was no significant difference between the EoE and PPI-REE groups in regard to those values.

Various symptoms reported by the patients are also shown in Table 1. In patients with EoE and PPI-REE, the most frequently reported was dysphagia (72.7 and 43.8 %, respectively), while only 28.2 % of the RE patients reported that. The frequency of dysphagia was not significantly different between the EoE and PPI-REE groups. Heartburn was reported by approximately one-third of the patients in the EoE, PPI-REE, and RE groups, while acid regurgitation was only reported by patients with RE or PPI-REE. Of 39 patients with RE, 14 (35.9 %) had no symptoms, while all patients with EoE and PPI-REE had symptoms of esophageal dysfunction. We next compared the symptoms of symptomatic RE patients (*n* = 25) with those of other groups. The frequency of dysphagia was still higher in the EoE than the symptomatic RE group (72.7 vs. 44.0 %). Heartburn was more frequently reported in symptomatic RE than the EoE and PPI-REE groups (48.0, 36.4, and 37.5 %, respectively), though the difference was not statistically significant. Atopic background was also compared among the groups. Allergic diseases were noted in 81.8 % of the patients with EoE, with lower frequencies seen in the PPI-REE and RE groups. Only 17.9 % of the RE patients reported an atopic background. Bronchial

Table 1 Clinical characteristics of EoE, PPI-REE, and RE cases

	Age	Male/female	Height (cm)	Weight (kg)	BMI
EoE (n = 11)	46 ± 5 ^b	10/1	169 ± 4	71 ± 9	25 ± 2
PPI-REE (n = 16)	48 ± 3 ^c	16/0 ^c	164 ± 1 ^c	66 ± 2 ^c	24 ± 1 ^c
RE (n = 39)	64 ± 2	24/15	161 ± 2	61 ± 2	23 ± 1

	Atopic background									
	Symptoms									
Dysphagia	Heartburn	Acid regurgitation	Chest pain	Others	Asthma	Rhinitis	Atrophic dermatitis	Food allergy	Any	
EoE (n = 11)	8 (72.7 %) ^b	4 (36.4 %)	0 (0 %)	2 (18.2 %)	4 (36.4 %) ^{a,b}	6 (54.5 %) ^b	3 (27.3 %) ^b	3 (27.3 %) ^{a,b}	9 (81.8 %) ^b	
PPI-REE (n = 16)	7 (43.8 %)	6 (37.5 %)	3 (18.8 %)	2 (12.5 %)	2 (12.5 %)	9 (56.3 %) ^c	2 (12.5 %)	0 (0 %)	11 (68.8 %) ^c	
RE (n = 39)	11 (28.2 %)	12 (30.8 %)	10 (25.6 %)	2 (5.1 %)	6 (15.4 %)	3 (7.7 %)	1 (2.6 %)	0 (0 %)	7 (17.9 %)	

EoE eosinophilic esophagitis, PPI-REE proton-pump inhibitor-responsive esophageal eosinophilia, RE reflux esophagitis

^a *P* < 0.05 between EoE and PPI-REE

^b *P* < 0.05 between EoE and RE

^c *P* < 0.05 between PPI-REE and RE

Table 2 Laboratory test results for EoE, PPI-REE, and RE cases

	Leucocytes (/μl)	Eosinophils (/μl)	CRP (mg/dl)	Total IgE (IU/ml)
EoE (<i>n</i> = 11)	5955 ± 426	569 ± 175 ^b	0.3 ± 0.2	640 ± 134 ^a
PPI-REE (<i>n</i> = 16)	5747 ± 400	314 ± 69	0.1 ± 0.0	400 ± 185
RE (<i>n</i> = 39)	5766 ± 324	202 ± 26	0.2 ± 0.1	–

EoE eosinophilic esophagitis, *PPI-REE* proton-pump inhibitor-responsive esophageal eosinophilia, *RE* reflux esophagitis

^a *P* < 0.05 between EoE and PPI-REE

^b *P* < 0.05 between EoE and RE

^c *P* < 0.05 between PPI-REE and RE

asthma, a typical allergic disease accompanying esophageal eosinophile infiltration, was found in 36.4 % of the EoE patients, 12.5 % of those with PPI-REE, and 2.6 % of those with RE. Food allergies were found only in EoE patients. Thus, PPI-REE was considered to be ranked between RE and EoE in terms of frequency of accompanying allergic diseases, though the only significant differences between the EoE and PPI-REE groups were in regard to asthma and food allergies.

Laboratory test results

The results of laboratory testing are shown in Table 2. The numbers of peripheral leucocytes and eosinophils tended to be higher in patients with EoE as compared to the others. However, the differences between EoE and PPI-REE were not significant. In contrast, plasma total IgE concentration was significantly higher in the EoE group as compared to the PPI-REE group.

Endoscopic findings

Esophageal mucosal longitudinal furrows, multiple concentric rings, and white plaque were more frequent in the EoE and PPI-REE groups as compared to RE (Table 3). Notably, there was a significantly increased prevalence of longitudinal furrows and of white plaque in the EoE and PPI-REE groups, and these findings were considered to be specific for diagnosis in those patients. However, there was no significant difference between EoE and PPI-REE in regard to endoscopic findings.

Esophageal mucosal redness and edema were more frequently found in patients with RE as compared to the others, and RE patients had a significantly higher prevalence of mucosal edema. Again, there were no significant differences between EoE and PPI-REE for these endoscopic findings.

Various grades of mucosal break were found in all patients with RE and 3 (18.8 %) patients with PPI-REE, while no such breaks were found in the EoE patients. Mucosal breaks were cured by a standard dose of PPI

within a 2-month administration period in all patients with PPI-REE. Hiatal hernias were found only in patients with RE. Thus, both mucosal breaks and hiatal hernias were more frequently found in the RE group as compared to the others. Gastric mucosal atrophy was found at the lowest frequency in the EoE patients, followed in order by PPI-REE and RE, though the differences among the groups were not significant.

Thus, longitudinal furrows and white plaque—typical findings of esophageal eosinophile infiltration—were found at similar frequencies in the EoE and PPI-REE patients, while the occurrence rates for mucosal breaks and gastric mucosal atrophy in the PPI-REE group were between those of the EoE and RE groups.

Histopathological findings for biopsy specimens

Histopathological findings, including number of infiltrating eosinophils in the esophageal mucosal epithelial layer, are shown in Table 4. The number of biopsies of each group [mean ± SD (range)] was as follows: EoE, 3.3 ± 1.2 (2–6); PPI-REE, 2.9 ± 0.6 (2–4); RE, 2.0 ± 0.7 (1–4), indicating that the number of biopsies in the RE group was lower than those in the other groups. Dense eosinophile infiltration was found in the EoE and PPI-REE groups, and the number of eosinophils was also similar in both groups. On the other hand, only a small number of infiltrating eosinophils was found in the RE patients.

Lymphocyte infiltration, basal cell hyperplasia, and spongiosis were also found more frequently in patients with EoE and PPI-REE as compared to those with RE. There was no difference in regard to basal cell hyperplasia and spongiosis between the EoE and PPI-REE groups.

Our histopathological examinations of biopsy specimens did not reveal any remarkable differences between EoE and PPI-REE.

Multivariate analysis for the prediction of EoE

In order to find predictive factors for diagnosing EoE, multivariate logistic regression analysis was performed. In

Table 3 Endoscopic findings in EoE, PPI-REE, and RE cases

	Longitudinal furrows		Concentric rings		White plaque	Stricture	Mucosal redness	Edema
EoE (n = 11)	9 (81.8 %) ^b		3 (27.3 %)		8 (72.7 %) ^b	0 (0 %)	0 (0 %)	3 (27.3 %) ^b
PPI-REE (n = 16)	16 (100 %)		5 (31.3 %)		7 (43.8 %) ^c	0 (0 %)	0 (0 %)	3 (18.8 %) ^c
RE (n = 39)	0 (0 %)		4 (10.3 %)		0 (0 %)	0 (0 %)	8 (20.5 %)	25 (64.1 %)
Mucosal breaks								
A	B	C	D	Any	Presence of hiatal hernia	Absent	Closed type (C1-3)	Open type (O1-3)
EoE (n = 11)	0 (0 %) ^b	0 (0 %) ^b	0 (0 %)	0 (0 %) ^b	0 (0 %)	7 (63.6 %)	3 (27.3 %)	1 (9.1 %)
PPI-REE (n = 16)	1 (6.3 %) ^c	2 (12.5 %) ^c	0 (0 %)	0 (0 %)	0 (0 %) ^c	7 (43.8 %)	9 (56.3 %)	0 (0 %)
RE (n = 39)	20 (51.3 %)	17 (43.6 %)	1 (2.6 %)	39 (100 %)	8 (20.5 %)	14 (35.9 %)	15 (38.5 %)	10 (25.6 %)

EoE eosinophilic esophagitis, PPI-REE proton-pump inhibitor-responsive esophageal eosinophilia, RE reflux esophagitis

^a $P < 0.05$ between EoE and PPI-REE

^b $P < 0.05$ between EoE and RE

^c $P < 0.05$ between PPI-REE and RE

EoE patients, significantly higher prevalences of an atopic background with asthma and of food allergy as well as a higher concentration of plasma total IgE were confirmed by the univariate analysis, although these differences were not found to be statistically significant in a multivariate regression analysis (data not shown). These data were consistent with previous report conducted in Western countries [11, 13].

Discussion

In the present study, we examined the clinical, endoscopic, and histopathological results of patients with EoE, PPI-REE, and RE, and compared our findings. In cases with an esophageal eosinophilia, 59 % of the cases responded to PPI administration and were diagnosed with PPI-REE in this study. There were no remarkable differences between the patients with EoE and PPI-REE in regard to endoscopic and histopathological examination findings, whereas there were some differences in regard to clinical characteristics between those groups, as the EoE patients had a stronger atopic background including allergic comorbidities and elevated IgE.

Esophageal epithelial eosinophile infiltration is a pathological condition that causes unpleasant esophageal symptoms, including dysphagia, as well as esophageal stenosis after long-lasting inflammation [1, 19]. For a first-line therapy, an elimination diet that excludes milk, wheat, egg, soy, nuts, and seafood has been reported, while topical esophageal glucocorticoid administrations have also been used [29–32]. These have been found to be effective in many cases, though they have some limitations, including inconvenience, adverse effects, and nonuniversal effect [33, 34].

A recent study found that nearly half of the analyzed patients with esophageal eosinophilia responded to PPI administration [9]. Since PPIs show few clinically important or serious side effects, they are widely used to treat the disease [35]. In Asian countries, cases of PPI-responsive esophageal eosinophilia have been reported to be around 50 % of the cases with esophageal eosinophilia [36–39]. In this study, 59 % of the cases responded to PPI administration, confirming previous reports from many countries. A recently presented consensus recommendation proposes the division of esophageal eosinophilia into two categories, EoE and PPI-REE [1, 19], based on clinical and pathological responses to PPI administration. When clinical and histopathological characteristics and gene expression patterns of EoE and PPI-REE were compared in Western countries, they were found to have similar abnormalities, making differentiation of these categories difficult prior to prescribing a PPI [11–14]. One of those reports suggested

Table 4 Histopathological findings in the EoE, PPI-REE, and RE cases

	Eosinophils/HPF	Lymphocytes/HPF	Neutrophils/HPF	Presence of		
				Basal cell hyperplasia	Balloon cells	Spongiosis
EoE (<i>n</i> = 11)	48.6 ± 9.0 ^b	15.0 ± 1.8 ^{a,b}	0	9 (81.8 %) ^b	1 (9.1 %)	9 (81.8 %) ^b
PPI-REE (<i>n</i> = 16)	48.3 ± 9.5 ^c	29.3 ± 4.8 ^c	0	12 (75.0 %) ^c	1 (6.3 %)	12 (75.0 %) ^c
RE (<i>n</i> = 39)	1.5 ± 0.4	11.0 ± 1.6	0	16 (41.0 %)	11 (28.2 %)	0 (0 %)

EoE eosinophilic esophagitis, PPI-REE proton-pump inhibitor-responsive esophageal eosinophilia, RE reflux esophagitis

^a *P* < 0.05 between EoE and PPI-REE

^b *P* < 0.05 between EoE and RE

^c *P* < 0.05 between PPI-REE and RE

an increased presence of esophageal erosions and hiatal hernias and a decreased presence of longitudinal furrows, rings, and peripheral eosinophilia in patients with PPI-REE as compared to those with EoE [11], while others did not find those differences [12, 13]. Therefore, clinical and esophageal abnormalities in cases of esophageal eosinophilia are considered to be unreliable as prognostic markers to predict possible response to PPI administration [11]. One report suggested that the gene expression of the potassium channel *KCNJ2* differs between EoE and PPI-REE, though this result was not confirmed by other investigators [14].

In the present study, we investigated both esophageal histopathological and systemic clinical findings to reveal abnormalities that may predict a positive response to PPI treatment in Japanese patients with esophageal eosinophilia. In addition, patients with RE were also included in the study population, as they show a favorable response to PPIs.

As previously reported, patients in both the EoE and PPI-REE groups had dense esophageal eosinophile infiltration, though there was no difference in regard to eosinophile density between those pathological conditions. RE patients showed weak eosinophile infiltration. Since no prospective histological study has been done in cases with RE, our study investigating eosinophile infiltration is important even though the study is a retrospective one [35]. Similar to the amount of eosinophile infiltration, lymphocyte infiltration was greater in the EoE and PPI-REE patients as compared to those with RE. Also, patients with PPI-REE showed a higher lymphocyte infiltration density than those with EoE, but the mechanism driving this difference was not clear. Since the difference was not remarkable, and there was a significant overlap between the EoE and PPI-REE groups, lymphocyte infiltration may not be an effective predictive marker of PPI responsiveness. Furthermore, there were no differences in regard to epithelial basal cell hyperplasia, balloon cells, and spongiosis between these groups.

When endoscopic findings were compared between EoE and PPI-REE, no statistically significant difference was

found, whereas there were remarkable differences between the combination of the EoE and PPI-REE groups and the RE group. The only difference noted between the EoE and PPI-REE groups was that 18.8 % of patients in the latter had mucosal breaks suggesting comorbid RE, though the difference was not significant. It was recently reported that 20 % of patients with PPI-REE showed reflux esophagitis in endoscopy findings, in addition to typical findings suggesting esophageal eosinophile infiltration [40], which is supported by the present results. The mechanisms through which PPI relieves esophageal eosinophilia are not yet clarified. A recent report suggested that cases with abnormal gastroesophageal acid reflux responded favorably to the PPI therapy, in agreement with our study [41].

In our comparisons of reported symptoms, patients with PPI-REE were found to have acid regurgitation, suggesting the presence of gastroesophageal acid reflux. Other reports have also suggested that up to two-thirds of patients with PPI-REE have pH monitoring-proven pathological gastroesophageal acid reflux [42]. Thus, PPI-REE cases are considered to have an increased risk of gastroesophageal acid reflux as compared with EoE, though signs and symptoms suggesting gastroesophageal acid reflux were found only in a small percentage of our patients with PPI-REE.

We also compared the atopic backgrounds of the EoE and PPI-REE groups, which showed that the former group had more frequent allergic comorbidities, a higher eosinophile count in peripheral blood, and elevated total IgE in plasma. Therefore, allergic conditions were more apparent in cases with EoE as compared to those with PPI-REE, whereas the similarities and differences in allergic conditions between two entities remain obscure based on previous studies conducted in Western countries [43, 44].

From our observations, we speculate that an allergic condition, such as a high count of peripheral eosinophils, a high plasma IgE level, and an atopic background, indicates a poor response to PPIs in patients with esophageal eosinophilia. On the other hand, acid regurgitation and the presence of esophageal mucosal breaks may suggest a

favorable response to PPI administration. Although our results suggest these possibilities, the differences between the EoE and PPI-REE cases were marginal, and there were no independent clinical, endoscopic, or histological predictors that reliably distinguished PPI-REE from EoE in multivariate analysis. In a recent review, it was proposed that PPI responsiveness should not be used as a diagnostic tool, so it was recommended that the use of the term PPI-REE should be avoided in updated diagnostic criteria [35]. In addition, the dose and duration of an adequate initial PPI trial should be determined. Nevertheless, these and other factors that are possible predictive factors for the response of patients with eosinophilia to PPI administration require further investigation.

There are some limitations to our study. The numbers of patients with EoE and PPI-REE may not have been adequate, even though we enrolled all patients with esophageal eosinophilia treated at our institution over the past 10 years. Most of the patients with esophageal eosinophilia were treated and evaluated with a standard-dose PPI. A larger multicenter prospective study will be necessary to obtain conclusive results regarding predictive factors related to PPI responsiveness at a high dose. In addition, there may have been some inclusion bias in regard to the enrolled patients with RE, since biopsy specimens were only obtained from a small percentage of that group, and the number of biopsies was lower than those in the EoE or PPI-REE groups, while all of the patients with EoE and PPI-REE had such specimens available.

In conclusion, our comparisons of the clinical, endoscopic, and histopathological findings of patients with EoE, PPI-REE, and RE revealed nearly no difference in esophageal mucosal histopathological findings between those with EoE and PPI-REE. On the other hand, the present clinical findings suggest that patients with EoE are more prone to comorbid allergic diseases. Additional studies are necessary to reveal predictive factors for PPI responsiveness in patients with esophageal eosinophilia.

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Compliance with ethical standards

Conflict of interest Yoshikazu Kinoshita has received research grants from AstraZeneca K.K., Daiichi Sankyo Co., Ltd., Eisai Co., Ltd., and Takeda Pharmaceutical Co., Ltd. and has performed speaking and teaching commitments for AstraZeneca K.K., Daiichi Sankyo Co., Ltd., Eisai Co., Ltd., and Takeda Pharmaceutical Co., Ltd. The following authors have nothing to declare: Dijin Jiao, Norihisa Ishimura, Riruke Maruyama, Noriyoshi Ishikawa, Mamiko Nagase, Naoki Oshima, Masahito Aimi, Eiko Okimoto, Hironobu Mikami, Daisuke Izumi, Mayumi Okada, Shunji Ishihara.

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