

Original Article

Do endoscopic features suggesting eosinophilic esophagitis represent histological eosinophilia?

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Background: Esophageal linear furrows, corrugated rings, and/or white exudates are often seen in patients with eosinophilic esophagitis (EoE); however, whether these are specific to EoE remains unclear. Endoscopic surveillance of these features was conducted to determine whether these represent esophageal eosinophilia, which is essential for the diagnosis of EoE.

Patients and Methods: Two thousand seven hundred and sixty-three patients were enrolled consecutively. Target biopsy was carried out when the above features were seen. Histological eosinophilia was defined as 24 or more eosinophils per high-power field (HPF). Associations between features and eosinophilia were analyzed statistically.

Results: Two thousand five hundred and forty-five patients completed the study. Linear furrows, corrugated rings and white exudates were seen in 24, 15 and 45 patients, respectively. These findings somewhat overlapped. Among 58 biopsied patients with

any of the above features, these features represented eosinophilia in 14% (3/21), 23% (3/13), and 5% (2/43), respectively. None of the 199 patients who received biopsy for other features had eosinophilia. Two of five eosinophilia patients were diagnosed with EoE. Multiple comparisons revealed that eosinophil counts in linear furrows and corrugated rings but not white exudates were significantly greater than those in other features (12, 9, 1, and <1 eosinophils/HPF on average, respectively).

Conclusions: An endoscopic feature suggesting EoE does not always represent esophageal eosinophilia and is non-specific for EoE, although it reminds endoscopists of the presence of EoE. The diagnostic utility of linear furrows or corrugated rings for esophageal eosinophilia is superior to that of white exudates.

Key words: atopy, endoscopy, eosinophilic esophagitis, esophageal eosinophilia, histology

INTRODUCTION

EOSINOPHILIC ESOPHAGITIS (EOE) is a chronic condition characterized clinically by symptoms related to esophageal dysfunction, and histologically by eosinophil-predominant inflammation of the esophagus.^{1,2} EoE patients often have concurrent atopic diatheses such as asthma, and the pathophysiological mechanisms are presumed antigen-driven, aberrant immunological responses on the esophageal mucosa.¹ Although avenues available for the diagnosis of EoE have been searched based on such a pathogenesis, no unique marker of EoE has been found. Therefore, current diagnostic criteria for EoE require the following clinico-pathological conditions: clinical esophageal symptoms,

histological esophageal eosinophilia, and exclusion of other possible causes of esophageal eosinophilia.^{1,2} Although endoscopic findings of EoE are not indispensable for the diagnosis, the classic features of longitudinal/linear furrows, circular/concentric/corrugated rings, or white exudates on the esophageal mucosa are often encountered during endoscopic examinations of EoE patients. Pooled analysis showed that at least one such feature was detected by endoscopy in up to 93% of EoE;³ therefore, such features may be helpful for the diagnosis.

Whether these endoscopic features are specific to EoE remains unclear because prospective surveillance of each feature is scarce, and the relationship between each feature and esophageal eosinophilia, which is essential for the diagnosis of EoE, has not been prospectively examined. The aim of the present study was to determine whether these features are specific for EoE (i.e. whether these features are available as unique markers for the diagnosis) or whether these features represent esophageal eosinophilia (i.e. whether these

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features are appropriate diagnostic criteria). We conducted prospective endoscopic surveillance of such features, and histologically examined the degree of eosinophilic infiltration classed by endoscopic features.

METHODS

Patients

THIS WAS A prospective, cross-sectional, observational study that was conducted at our hospital. Consecutive patients who underwent upper gastrointestinal endoscopy, except for emergency or therapeutic endoscopy, were enrolled in this study between November 2010 and October 2012. Endoscopists interviewed patients about atopic diseases and proton pump inhibitor (PPI) use prior to endoscopy as follows: ‘Have you ever suffered from asthma, atopic dermatitis, or pollinosis, at least once in either the past or the present?’ and ‘Have you continuously taken a drug once a day to suppress gastric acid for more than the last month?’ (PPI has been approved for use only once a day with a few exceptions in Japan, and H₂ receptor blocker is used twice a day usually. Medical records were also referred to.) Reasons for endoscopy were examined using our computerized endoscopic database or electronic medical record system. Exclusion criteria were repeat endoscopy within 6 months in previously enrolled patients in the present study to avoid duplication, patients with esophagectomy or advanced esophageal cancer, steroid or immunosuppressant users, and communication difficulty. This study was approved by our institutional review board, and informed consent was obtained from all the patients.

Endoscopy

Experienced endoscopists (K.H., J.W., H.F., J.T., T.T., J.S., T.K., T.O., F.T., T.Y., T.O.) became familiar with the endoscopic features associated with EoE before the present study:

linear furrows, corrugated rings, and white exudates, using images in previous reports.^{2,4,5} Definitions of these features are summarized in Table 1 on the basis of the consensus-meeting criteria.^{1,2} When such features were seen and were similar to the images in the above reports, at least two target biopsy specimens from the upper and lower esophagus were obtained according to a recommendation.⁶ In addition, two biopsy specimens from the gastric antrum and the descending part of the duodenum were obtained to exclude eosinophilic gastroenteritis, because its exclusion is essential for the diagnosis of EoE. When it was hard to distinguish the above features from endoscopic features of reflux esophagitis or monilial esophagitis as shown in Table 1, these were included in EoE-related features, and at least one esophageal biopsy specimen was obtained to make the differential diagnosis. When patients had unexplained dysphagia or refractory reflux-like symptoms, at least one esophageal biopsy specimen was obtained, even if EoE-suggesting features were not seen. The presence of reflux esophagitis was recorded according to the Los Angeles classification,⁷ which was considered when the grade was $\geq$ A. The presence of monilial esophagitis was considered when multiple, raised, white spots, which were generally larger than the white exudates associated with EoE, were observed on the esophageal mucosa. This surveillance was conducted mainly using a high-resolution endoscope (GIF-H260; Olympus, Tokyo, Japan).

Diagnosis

The formalin-fixed biopsy specimens were cut and stained with hematoxylin and eosin. The histological diagnosis of esophageal eosinophilia was made by a single pathologist (K.H.) when the highest number of intraepithelial eosinophils in the esophagus within a high-power field (HPF) of 0.24 mm² excluding the subepithelial layer (mucosal lamina propria), the so-called peak count in the densest area, was

Table 1 Definitions of endoscopic terms related to eosinophilic esophagitis

Term [†]	Definition	Exclusion diagnosis
Linear furrows	Shallow furrows extending along the long axis of the esophagus	Reflux esophagitis [‡]
Corrugated rings	Esophageal transient or persistent (fixed), multiple stenoses having a common axis	Reflux esophagitis [§]
White exudates	Finely granular, white exuded matter on the esophageal mucosa	Monilial esophagitis [¶]

[†]Terms related to eosinophilic esophagitis were not used when these features seemed to be obviously caused by reflux esophagitis, where linear furrows and corrugated rings mimic the mucosal break and stenosis, respectively, or monilial esophagitis, where white exudates mimic fungal white matter.

[‡]Mucosal breaks of grade B in the Los Angeles classification, which are atypically located on the esophagus other than the cardiac region, without concomitant feature of corrugated rings or white exudates.

[§]Mucosal breaks with transient rings, which are considered to be developed as a result of longstanding gastroesophageal reflux, as shown in Figure 2.

[¶]Mild candidiasis, which is observed as a small number of finely granular, subtly raised spots on a focal area, as shown in Figure 3.

≥24. Gastroduodenal eosinophilia was considered when the highest number of eosinophils within the HPF was ≥60. If neoplasms such as dysplasia or carcinoma were contained in the biopsy specimen, it was excluded from histological analyses.

The diagnosis of EoE was made when all of the following consensus-meeting criteria were fulfilled: (i) symptoms related to esophageal dysfunction, such as dysphagia or unexplained heartburn; (ii) esophageal eosinophilia; and (iii) the absence of other disorders associated with esophageal eosinophilia, such as gastroesophageal reflux disease or eosinophilic gastroenteritis.^{1,2}

Statistics

Data are shown as the mean ± standard deviation. Fisher's exact probability test or the Wilcoxon test was used to compare two variables. Steel's test (a non-parametric test) was used for multiple comparisons. All tests of significance were two-tailed, and $P < 0.05$ was considered significant. All analyses were done using JMP 10 software (SAS Institute Inc., Cary, NC, USA).

RESULTS

Patients

TWO THOUSAND SEVEN hundred and sixty-three patients were enrolled, but 218 (8%) patients were excluded for the following reasons: steroid use in 104 patients, 48 recent repeat endoscopy, 26 communication difficulty, 14 incomplete recordings, 11 immunosuppressant use, 10 post-esophagectomy, and five advanced esophageal cancer. Reasons for endoscopy in the remaining 2545 patients were as follows: screening in 764 patients (30%), symptoms in 640 (25%), including 176 epigastric pain etc., follow up of disease in 884 (35%) including 150 peptic ulcer diseases etc., and suspected disease in 257 (10%). Patient demographics are summarized in Table 2.

Endoscopy

Thirteen of 2545 patients had typical endoscopic features of linear furrows ($n = 7$), corrugated rings ($n = 6$), or white exudates ($n = 8$) (Figs 1–3), and these features somewhat overlapped. Forty-nine patients had similar features that required differential diagnosis from reflux or monilial esophagitis. All of the former 13 patients and 45 of the latter 49 patients except four anticoagulant users received esophageal target biopsy, 2.7 ± 0.9 (range, 2–4) and 1.3 ± 0.5 (1–3), respectively. The overlap among these endoscopic features in 58 biopsied patients is shown in Figure 4.

Table 2 Demographic characteristics of the eligible patients

Characteristics	Patients ($n = 2545$) (%)
Age (years) [range]	62 ± 15 [13–98]
Males	1397 (55)
PPI user	548 (22)
Atopic diathesis	
Pollinosis	500 (20)
Asthma	125 (5)
Atopic dermatitis	80 (3)
Any of the above	609 (24)
Endoscopic diagnosis	
Reflux esophagitis	268 (11)
Monilial esophagitis	67 (3)
Endoscopic features	
Linear furrows	24 (1)
Corrugated rings	15 (1) [†]
White exudates	45 (2)
Any of the above	62 (2)
Esophageal eosinophilia [‡]	5 (0.2)
Fulfilling EoE criteria	2 (0.08)

[†]Ratio of transient/fixed rings was 14/1.

[‡]Patient number examined histologically was 257.

EoE, eosinophilic esophagitis; PPI, proton pump inhibitor.

Histology

Esophageal eosinophilia was recognized in four of 13 patients with typical endoscopic features suggesting EoE and in only one of 45 patients with similar endoscopic features that required differential diagnosis. Proportions of esophageal eosinophilia classed by endoscopic features are shown in Figure 4. Although reasons for the absence of eosinophilia despite endoscopic features suggesting EoE were unknown in the majority of patients, fungus was histologically recognized in 12 of 43 biopsied patients with white exudates.

One hundred and ninety-nine patients without endoscopic features suggesting EoE received esophageal biopsy because of other endoscopic features or esophageal symptoms, including 43 dysphagia and 48 heartburn, but none had eosinophilia. The distribution of peak values of eosinophil counts is shown in Figure 5. The count was ≤4 in most patients (245/257 [95%]).

Comparisons of eosinophil counts classed by esophageal endoscopic features are shown in Figure 6. Multiple comparisons revealed that the eosinophil counts in linear furrows or corrugated rings were significantly greater than those in any endoscopic feature unrelated to EoE, but there were no statistical differences between white exudates and such features except normal mucosa ($P = 0.047$).

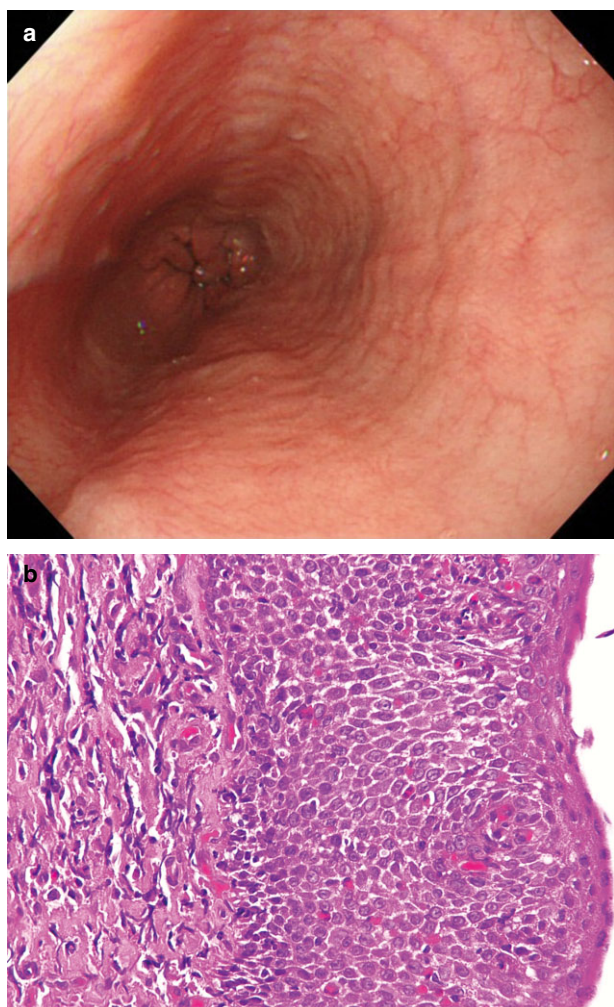


Figure 1 Eosinophilic esophagitis. (a) Subtle linear furrows and rings were observed endoscopically throughout the esophagus. (b) A number of eosinophils were histologically confirmed in the esophageal epithelium with basal cell hyperplasia and with sub-epithelial fibrosis, and these findings were consistent with typical eosinophilic esophagitis (hematoxylin-eosin stain, $\times 40$).

One of 45 patients who received gastroduodenal biopsy had gastroduodenal eosinophilia. This patient also had esophageal eosinophilia and then developed Crohn's disease.

Characteristics

Clinical comparisons of the five patients with and the 252 biopsied patients without esophageal eosinophilia are shown in Table 3. Patients with esophageal eosinophilia were significantly younger than those without. Patients with eosinophilia suffered from atopic dermatitis significantly more

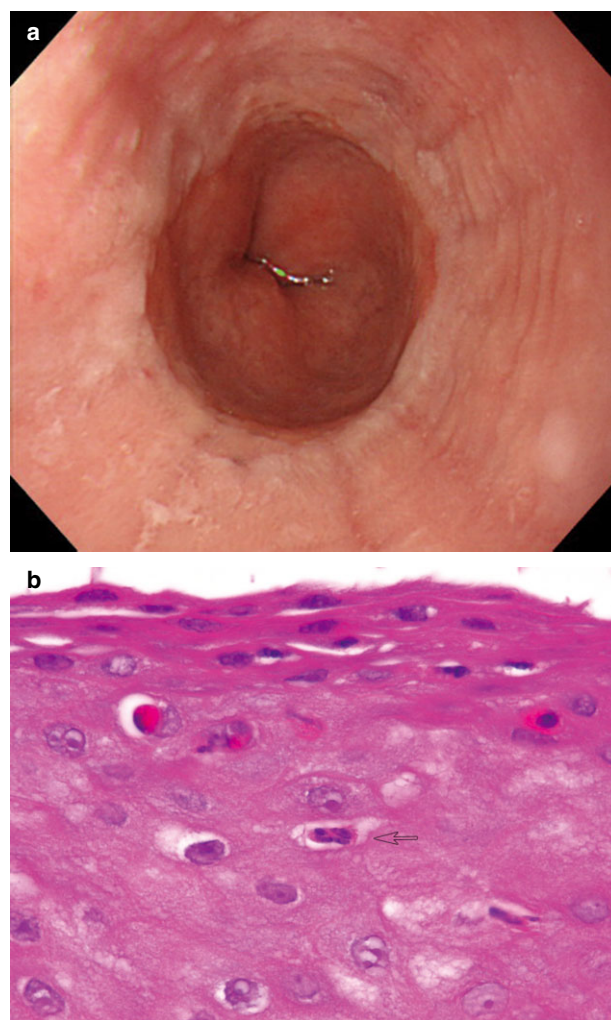


Figure 2 Gastroesophageal reflux disease. (a) Typical linear furrows and corrugated rings suggesting eosinophilic esophagitis were observed endoscopically with subtle white exudates in the lower esophagus. (b) A few neutrophils (arrow) were histologically confirmed in the esophageal epithelium with several eosinophils (peak count of 14 eosinophils/high-power field) (hematoxylin-eosin stain, $\times 100$). Such low-grade eosinophilia disappeared after proton pump inhibitor medication, considering that it had been due to gastroesophageal reflux.

frequently than those without. Esophageal linear furrows and corrugated rings were observed significantly more frequently in patients with eosinophilia than in those without; however, white exudates were observed at a similar frequency.

Of five patients with esophageal eosinophilia, two had no esophageal symptoms and one had Crohn's disease. The remaining two patients had PPI-refractory symptoms of

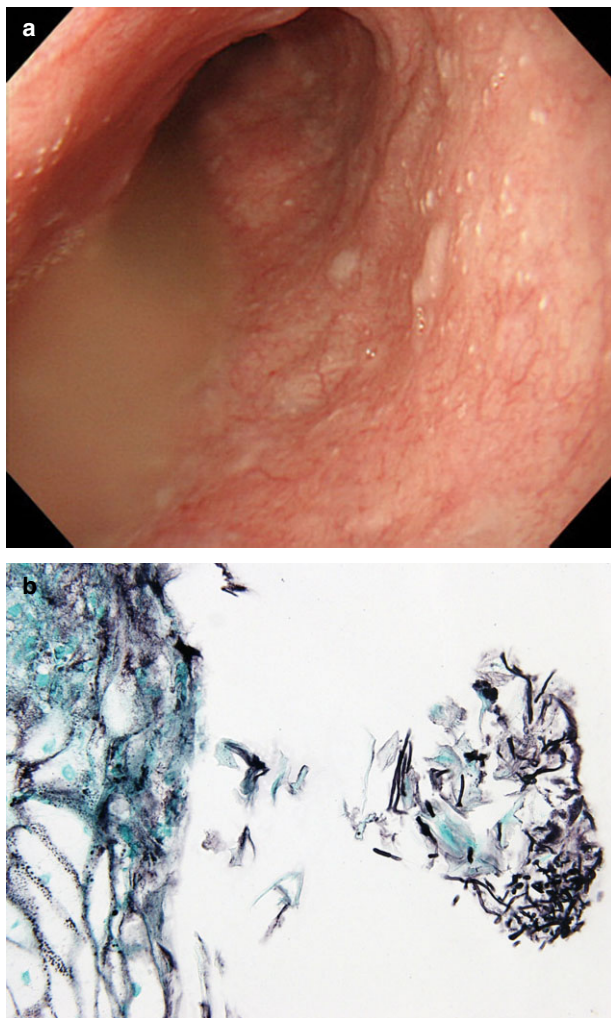


Figure 3 Monilial esophagitis. (a) Finely granular, white exudates were observed endoscopically in the middle esophagus, suggesting eosinophilic esophagitis except for the absence of a concomitant feature of linear furrows or corrugated rings. (b) Fungus was histologically recognized (Grocott's stain, $\times 40$). No eosinophilia was seen, although intraepithelial neutrophilia was seen (data not shown).

dysphagia without reflux esophagitis, and the histology of gastroduodenal biopsy specimens showed no evidence of eosinophilia; therefore, the diagnosis of EoE was made in only two (prevalence of 0.08%, 95% confidence interval of 0.02–0.29%) of 2545 patients. The two patients with EoE had perennial allergic rhinitis and one had comorbid pollinosis. The above two asymptomatic patients were considered to have subclinical EoE because they had no reflux esophagitis, PPI medication did not improve esophageal eosinophilia, and other possible causes of esophageal eosinophilia

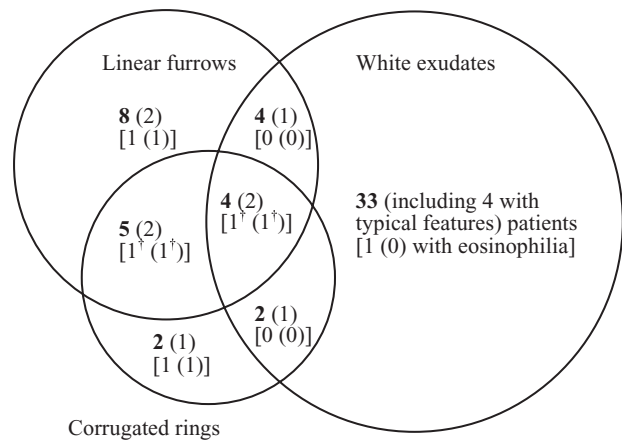


Figure 4 Patient numbers divided by endoscopic features suggesting eosinophilic esophagitis (EoE) ($n = 58$). Figures in brackets and parentheses are the number of patients with esophageal eosinophilia and with typical endoscopic features, respectively. †EoE.

were not found. The two patients had asthma and pollinosis, and one had comorbid atopic dermatitis.

Endoscopic features of linear furrows, corrugated rings, white exudates, and any of these features had sensitivities and specificities among the biopsied population for histological eosinophilia as follows: 14% (3/21) and 99% (234/236); 23% (3/13) and 99% (242/244); 5% (2/43) and 99% (211/214); and 9% (5/58) and 100% (199/199), respectively. These further reduced sensitivities and increased specificities for EoE as follows: 10% (2/21) and 100% (236/236); 15% (2/13) and 100% (244/244); 2% (1/43) and almost 100% (213/214); and 3% (2/58) and 100% (199/199), respectively.

DISCUSSION

AMONG CLASSIC EOE features, 14% (3/21) and 23% (3/13) of linear furrows and corrugated rings showed histological eosinophilia, respectively, whereas only 5% (2/43) of white exudates showed histological eosinophilia in the present study. This indicates that it is hard to distinguish white exudates seen in EoE from white matter seen in monilial esophagitis, as a result of the attachment of drugs, or with neutrophil aggregates in some types of esophagitis etc. Conversely, it may be relatively easy to distinguish linear furrows or corrugated rings seen in EoE from the mucosal break or stenosis seen in reflux esophagitis, respectively, because reflux esophagitis is often encountered in clinical practice and the distribution trend of the mucosal break or stenosis on esophageal mucosa is well recognized. These results may

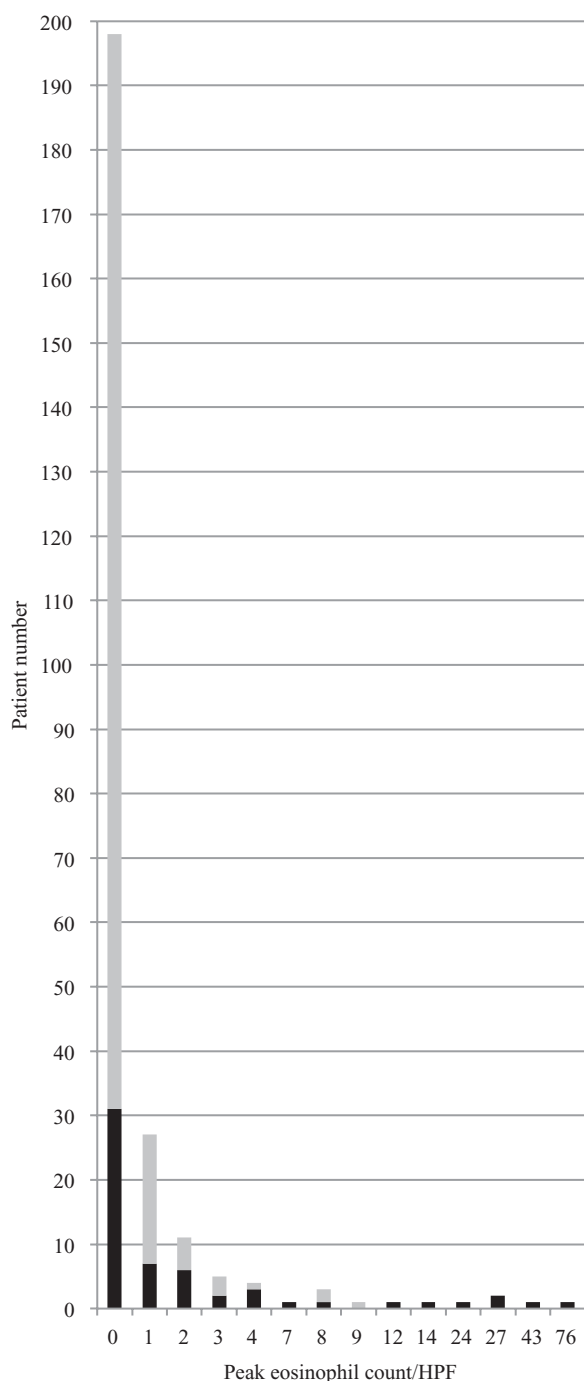


Figure 5 Distribution of esophageal eosinophil count ($n = 257$). Number of biopsy specimens was 1.6 ± 0.8 (range, 1–4) per patient in 58 patients with endoscopic features suggesting eosinophilic esophagitis (EoE) (■) and 1.4 ± 0.8 (1–5) in 199 patients without (□). None of four patients with eosinophilia except one patient with Crohn's disease had reflux esophagitis, whereas three patients with 9, 12 or 14 eosinophils/high power field (HPF) (so-called low-grade eosinophilia) had reflux esophagitis.

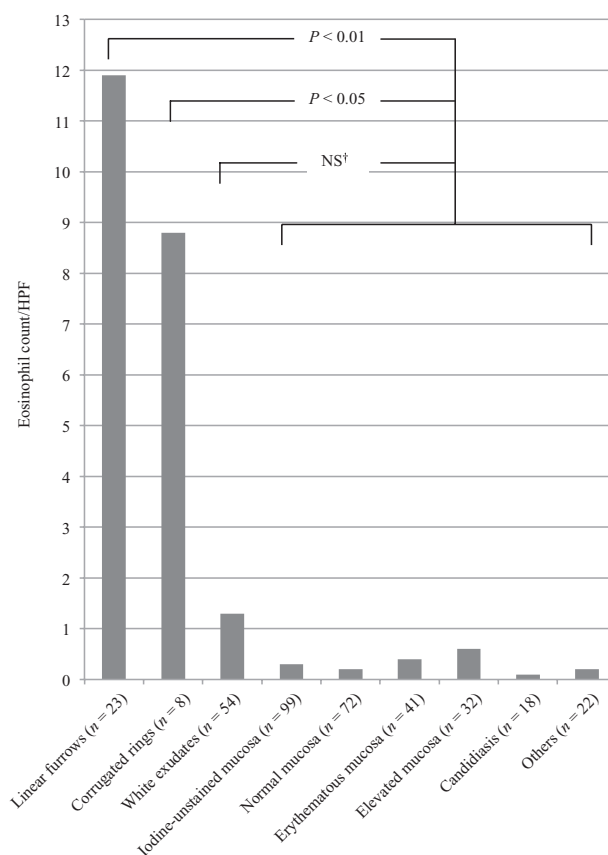


Figure 6 Peak eosinophil counts by esophageal endoscopic feature. Figures in parentheses are biopsy numbers ($n = 369$), not patient numbers. When multiple features overlapped, the most eye-catching feature was selected. Eosinophil counts were 11.9 ± 19.8 (range, 0–76) in linear furrows, which were observed in 15 patients; 8.8 ± 11.1 (0–27) in corrugated rings in seven patients; 1.3 ± 4.7 (0–33) in white exudates in 38 patients; 0.3 ± 1.1 (0–8) in iodine-unstained mucosa in 46 patients; 0.2 ± 1.0 (0–8) in normal mucosa in 60 patients; 0.4 ± 1.5 (0–9) in erythematous mucosa in 39 patients; 0.6 ± 1.8 (0–9) in elevated mucosa in 29 patients; 0.1 ± 0.2 (0–1) in candidiasis in 16 patients; and 0.2 ± 0.5 (0–2) in others in 16 patients. Biopsy of normal mucosa was done mainly for symptoms such as dysphagia in 20 patients ($n = 27$) or heartburn in 23 patients ($n = 30$), in which eosinophil count was up to 1 in each case. Sixteen erythematous mucosal biopsies in 16 patients were obtained from the mucosal break due to gastroesophageal reflux, while the eosinophil count was up to 9. †Except normal mucosa ($P = 0.047$). HPF, high-power field; NS, not significant.

reflect the results of an interobserver agreement study of the endoscopic findings of EoE; that is, fair to good for corrugated rings ($\kappa = 0.56$) and linear furrows ($\kappa = 0.48$), but poor for white exudates ($\kappa = 0.29$).⁸ As the majority of biopsies obtained from endoscopic features suggesting EoE showed

Table 3 Comparisons of 257 biopsied patients with and without esophageal eosinophilia

Parameter	Patients with eosinophilia (%) (n = 5)	Patients without eosinophilia (%) (n = 252)	P-value
Age (years) [range]	47 ± 16 [37–75]	63 ± 14 [13–90]	0.042
Males	4 (80)	159 (63)	NS
PPI user	2 (40)	77 (31)	NS
Atopic diathesis			
Pollinosis	3 (60)	63 (25)	NS
Asthma	2 (40)	18 (7)	NS*
Atopic dermatitis	2 (40)	17 (7)	0.046
Any of the above	4 (80)	76 (30)	0.034
Endoscopic diagnosis			
Reflux esophagitis	1 (20)	44 (17)	NS
Monilial esophagitis	0 (0)	19 (8)	NS
Endoscopic features			
Linear furrows	3 (60)	18 (7)	0.004
Corrugated rings	3 (60) [†]	10 (4)	0.001
White exudates	2 (40)	41 (16)	NS
Any of the above	5 (100)	53 (21)	<0.001

*P = 0.050.

[†]All three had transient rings.

NS, not significant; PPI, proton pump inhibitor.

no eosinophilia in the present study, these three classic features do not always seem to represent esophageal eosinophilia. The diagnostic utility of linear furrows and corrugated rings for esophageal eosinophilia is considered to be superior to white exudates. Our quantitative eosinophil counts were also shown to be higher in linear furrows and corrugated rings than white exudates.

Pooled analysis of several studies showed modest sensitivity for EoE, such as 48% for linear furrows, 44% for corrugated rings, and 27% for white exudates,³ whereas these sensitivities for EoE (esophageal eosinophilia with esophageal symptoms and exclusion of other disorders) in the present study were estimated as 10%, 15%, and 2%, respectively. The trend of lower sensitivity of white exudates was similar, but all values in the present study were lower than in the pooled analysis. As our study was prospective, even subtle mucosal abnormalities might be detectable, as shown in Figure 1; nevertheless, most features did not indicate EoE. This suggests that these classic features are non-specific to EoE, although they suggest EoE and remind endoscopists of the presence of EoE. Therefore, esophageal biopsy specimens should be obtained when EoE is suspected, regardless of the endoscopic features.

The cut-off value of ≥ 15 eosinophils per HPF is recommended for the diagnosis of EoE in consensus meetings;^{1,2} however, no studies have yet determined a validated threshold number that would define EoE and a standardized size of HPF.¹ Eosinophil counts per HPF vary a great deal depending on size; for example, the threshold number and size were

defined in previous studies as 15 eosinophils/0.53 mm² (equivalent to 7 eosinophils/0.24 mm² used in the present study),⁹ 20/0.55 (9/0.24),¹⁰ 15/0.4 (9/0.24),¹¹ 15/0.24,⁴ 15/0.15 (24/0.24),⁵ 20/0.19 (25/0.24),¹² 20/0.17 (28/0.24),¹³ or 30/0.24.¹⁴ Because of this, the often-used density of 24 eosinophils/0.24 mm² was applied in the present study. Consequently, as peak counts in 44 patients with reflux esophagitis were ≤ 14 , except for 27 in one patient with Crohn's disease and reflux esophagitis, as shown in Figures 2, 5 and 6, this seems to be suitable for the differential diagnosis from gastroesophageal reflux disease, and our results were similar even if 15/0.24 was applied.

Atopic dermatitis was associated with esophageal eosinophilia in the present study, and our two EoE patients had allergic rhinitis. A survey of EoE in Japan also showed that half of 26 patients with EoE had allergic diseases.¹⁵ This indicates a similar pathogenesis of EoE to Western patients. In Western endoscopic unselected patients, the highest prevalence of EoE was 6.5% (25/385) in the USA,¹² and the lowest prevalence was 0.4% (4/1000) in Sweden,¹⁶ and 0.5% (363/74 162) in the USA.¹⁴ Conversely, only two (0.08%) of 2545 patients were diagnosed with EoE during our surveillance, and the prevalence was similar to that in a recently reported endoscopic surveillance in Japan (4 of 23 346 [0.02%]).¹⁷ Severe EoE with fixed rings seems to develop from spread fibrosis with prolonged inflammation, which causes food impaction. As Japanese EoE patients with food impaction have not been reported,¹⁵ and neither of our two EoE patients had fixed rings and two asymptomatic patients

with eosinophilia (subclinical EoE) were found, EoE could be milder in Japanese patients than in Western patients. EoE represents an antigen-mediated disease.¹ As allergic disorders have increased in the pediatric Japanese population,^{18,19} EoE could increase in the future with the increase of allergic disorders in Japan.

The present study has some limitations. Esophageal biopsy number was small in patients who were weakly suspicious of EoE on moral and ethical grounds, because biopsy is an invasive procedure. Histological analysis showed diagnostic sensitivity for esophageal eosinophilia of 55% and nearly 80%, or 73% and 84%, when one or two biopsy specimens were obtained, respectively,^{5,11} although esophageal target biopsy was done using a high-resolution endoscope in the present study.

In summary, endoscopic features suggesting EoE do not always indicate histological eosinophilia and are non-specific to EoE, although they remind endoscopists of the presence of EoE. Esophageal biopsy specimens should be obtained when EoE is suspected, regardless of endoscopic features. The diagnostic utility of linear furrows and corrugated rings for esophageal eosinophilia is superior to white exudates. Patients with esophageal eosinophilia often have atopic characteristics, and EoE could increase in the future with the increase of allergic disorders in Japan.

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CONFLICT OF INTERESTS

AUTHORS DECLARE NO conflict of interests for this article.

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