

Original Article

Localized esophageal eosinophilia: Is it an early manifestation of eosinophilic esophagitis or a subtype of gastroesophageal reflux disease?

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Background and Aim: We recently encountered patients with localized esophageal eosinophilia in a small area of the esophagus. However, this condition remains to be described in detail, and its clinical significance has not been established. We investigated the clinical, endoscopic and histological features of localized esophageal eosinophilia in comparison with diffuse esophageal eosinophilia.

Methods: We investigated 10 patients with localized esophageal eosinophilia, and compared them with 23 who had diffuse esophageal eosinophilia. Whether esophageal eosinophilia was localized or diffuse was determined on the basis of endoscopic findings. Localized esophageal eosinophilia was defined endoscopically as a focal area of esophageal eosinophilia, whereas diffuse esophageal eosinophilia was defined as a widespread area of esophageal eosinophilia involving more than one of three locations: the upper, middle and lower esophagus. Histological esophageal eosinophilia in the mucosa showing endoscopic abnormality was confirmed by biopsy with a peak of ≥ 15 eosinophils/high-power field.

Results: There were no significant differences in age, gender distribution, allergic conditions or peripheral eosinophilia between the two groups. In all cases but one, localized esophageal eosinophilia was observed in a small area above the esophagogastric junction. Esophageal symptoms such as dysphagia, heartburn or chest pain were present in 20% of the localized group and in 65% of the diffuse group, the difference being statistically significant ($P < 0.05$). The maximum amounts of eosinophils infiltrating the esophageal mucosa did not differ between the groups.

Conclusions: Esophageal eosinophilia can be localized in a small area, especially above the esophagogastric junction. Gastric acid reflux or contact may influence this condition in addition to its allergic pathogenesis.

Key words: eosinophilic esophagitis, esophageal eosinophilia, gastroesophageal reflux disease (GERD)

INTRODUCTION

EOSINOPHILIC ESOPHAGITIS (EOE) is characterized by chronic inflammation with dense eosinophil infiltration into the esophageal mucosa, and is thought to be based on an allergic and immunological pathogenesis.¹ This condition is well known to be a common cause of feeding aversion, vomiting or regurgitation in young children, but, recently, it has been increasingly recognized in adults.^{2–4}

Adult EoE is typically manifested as dysphagia or food impaction and, often, heartburn, regurgitation or chest pain. Recent diagnostic guidelines for EoE have included the presence of clinical symptoms related to esophageal dysfunction, dense eosinophilic inflammation (≥ 15 eosinophils/high-power field [HPF]), unresponsiveness to potent acid-inhibitory therapy, and absence of abnormal acid reflux.¹

For diagnosis of EoE, recognition of the characteristic endoscopic features is important, and subsequent esophageal biopsy can also be carried out. In typical cases, several characteristic features such as linear furrows, concentric rings, white exudates or strictures are observed in the esophagus.¹ In a clinical setting, we have recently encountered some patients whose eosinophilic inflammation was

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localized to a very small area of the esophagus. Localized esophageal eosinophilia remains to be described in detail, and its clinical significance has not yet been established. In the present study, we investigated the clinical, endoscopic and histological features of localized esophageal eosinophilia in comparison with diffuse esophageal eosinophilia.

METHODS

A TOTAL OF 33 patients with esophageal eosinophilia were examined. Among them, 10 had the localized type and 23 had the diffuse type. The patients were diagnosed at five hospitals (Tohoku University Hospital, Miyagi Cancer Society, JR Sendai Hospital, Sendai Teishin Hospital and Yamagata University Hospital) between October 2006 and June 2012 during upper gastrointestinal endoscopy carried out as part of the work-up for gastrointestinal symptoms, or at annual check-ups for gastrointestinal malignancy. Irrespective of gastrointestinal symptoms, esophageal biopsies were done on any area of esophageal mucosa where esophageal eosinophilia was suspected, based on characteristic endoscopic features such as linear furrows, concentric rings and a white exudate.

Esophageal eosinophilia was confirmed histologically from at least one esophageal biopsy with a maximum of ≥ 15 eosinophils/high-power field (HPF).¹ One HPF was 0.24 mm^2 ($\times 40$ objective lens and $\times 10$ ocular lens, Olympus BX50 microscope; Olympus, Tokyo, Japan), and the number of esophageal eosinophils was determined in the HPF showing maximal infiltration. The distribution of endoscopic findings such as linear furrows, concentric rings and a white exudate was carefully reviewed and classified into localized or diffuse esophageal eosinophilia only on the basis of the macroscopic findings because of histologically patchy

eosinophil distribution.⁵ Localized esophageal eosinophilia was defined endoscopically as a partial or focal area of esophageal eosinophilia within one of three parts of the esophagus: upper, middle, and lower, as shown in Figures 1 and 2. Diffuse esophageal eosinophilia was defined as a widespread area of esophageal eosinophilia involving more than one of three parts of the esophagus: upper, middle, and lower. Esophageal symptoms (dysphagia, heartburn and chest pain), allergic conditions (bronchial asthma, atopic dermatitis or hay fever), peripheral eosinophilia (eosinophils $> 500/\mu\text{L}$) and use of antisecretory medications at the time of diagnosis of esophageal eosinophilia were checked on the basis of interview or access to medical charts. In addition, the degree of gastric mucosal atrophy, an indicator of gastric acid secretory function, was assessed endoscopically using the Kimura and Takemoto classification.⁶ Hypereosinophilic syndrome, eosinophilic gastroenteritis, or other causes of esophageal eosinophilia such as drugs, collagen disease or parasitic infection, were excluded. Patients with erosive esophagitis, diagnosed on the basis of the Los Angeles classification, were also excluded. This study was approved for submission and publication by the ethics committee of the Faculty of Medicine, Yamagata University.

Statistical analysis was carried out using the statistical software package, StatView 5.0 (Abacus Concepts, Berkeley, CA, USA) for Windows. Categorical variables of clinical demographics, or endoscopic and histological findings, were presented as proportions and analyzed using chi-squared test or Fisher's exact probability test. Continuous variables with skewed distributions such as patient age, number of esophageal biopsies and infiltrating eosinophils were presented as median (range) and analyzed using the Mann–Whitney *U*-test. Differences at $P < 0.05$ were considered to be statistically significant.

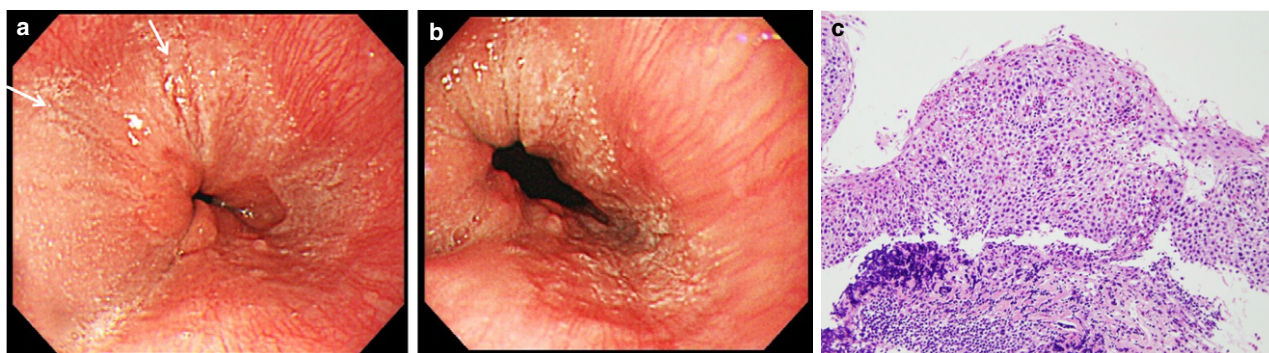


Figure 1 (a,b) Marked white exudates and a few linear furrows (white arrows) are localized just above the esophagogastric junction (35-year-old male asymptomatic patient). (c) Intense eosinophilic inflammation (189 eosinophils/high-power field) with a fibrotic lamina propria is shown in an esophageal biopsy sample.

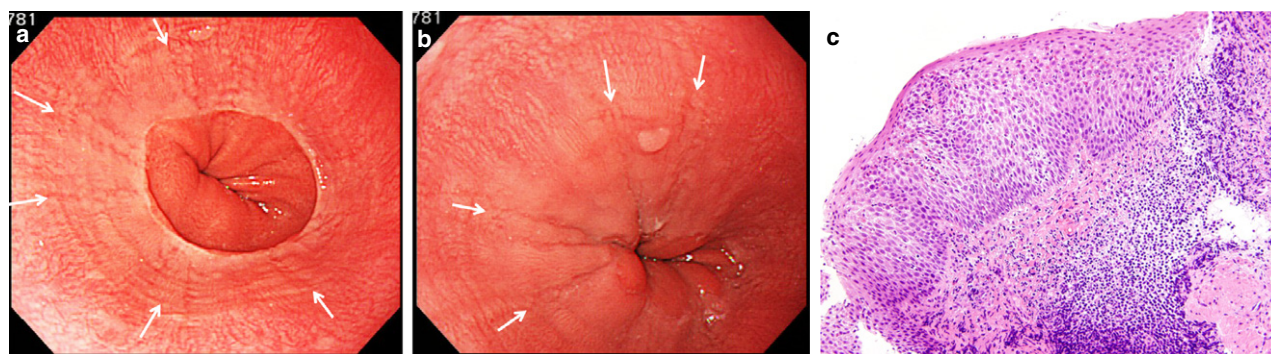


Figure 2 (a,b) Linear furrows (white arrows) and white turbidity is observed just above the esophagogastric junction (44-year-old male asymptomatic patient). (c) Intense eosinophilic inflammation (85 eosinophils/high-power field) with dilated intercellular spaces, with an accompanying fibrotic lamina propria, is shown in an esophageal biopsy sample.

RESULTS

PATIENT CHARACTERISTICS AND the endoscopic and histological findings in the 10 patients with localized esophageal eosinophilia are shown in Table 1. In all cases but one (case no. 5), eosinophilic inflammation was observed just above the esophagogastric junction (EGJ). In those cases, the longitudinal length exhibiting endoscopic abnormality was localized up to approximately 2 cm proximal from the EGJ. In three patients (nos. 6, 9 and 10), a small area of esophageal eosinophilia in the middle or lower esophagus was concurrently present. However, in the group of patients with diffuse esophageal eosinophilia, these endoscopic features were widely evident from the upper to the lower esophagus in 11 patients, from the middle to the lower esophagus in 11, and in the lower esophagus in one. Patients with localized type were significantly younger than those with diffuse type ($P < 0.05$). There was no significant difference in age, gender, allergic conditions or peripheral eosinophilia between the localized and diffuse esophageal eosinophilia groups (Table 2). A male predominance was found in both groups. Esophageal symptoms such as dysphagia, heartburn or chest pain were significantly less common in the localized group (20%) than in the diffuse group (65.2%) ($P < 0.05$). None of the patients in either group had a history of esophageal food or foreign body impaction. The number of esophageal biopsy samples obtained and the amounts of eosinophils infiltrating the esophagus showed no significant inter-group difference. Linear furrows were frequently observed in both groups (localized 100%, diffuse 78.3%). Concentric rings (localized 20%, diffuse 60.9%) and white exudates (localized 40%, diffuse 65.2%) were significantly more prevalent in the patients with diffuse esophageal eosinophilia than in those with localized esophageal eosinophilia. One patient in each

group had been taking a proton pump inhibitor (PPI) (rabeprazole 10 mg) at the time of diagnosis of esophageal eosinophilia. Absence of gastric atrophy was more common in the localized group (80%) than in the diffuse group (58%), but the difference was not statistically significant. One patient (case no. 2) was treated with a PPI (lansoprazole 30 mg) after diagnosis, and showed partial improvement symptomatically, endoscopically and histologically.

DISCUSSION

IN THE PRESENT study, we investigated the clinical characteristics of localized esophageal eosinophilia, which is an unknown condition. In the majority of the present cases, localized esophageal eosinophilia was found in a small area of the lower esophagus, especially above the EGJ. Comparison between patients with localized and diffuse esophageal eosinophilia revealed no significant differences in age, gender, allergic conditions, peripheral eosinophilia, endoscopic findings or the degree of histological eosinophilic infiltration. The localized type was also significantly less symptomatic than the diffuse type, suggesting that the extent of the esophageal mucosa affected by eosinophilic inflammation may be associated with the generation of esophageal symptoms such as dysphagia or heartburn.

It is interesting that in 90% of our patients, localized esophageal eosinophilia was present just above the EGJ, where gastric acid reflux is likely to impact. This observation suggests that localized esophageal eosinophilia above the EGJ may be a subtype of gastroesophageal reflux disease (GERD). It is also consistent with a proposed mechanism of esophageal eosinophilia in which esophageal mucosal damage by gastric acid reflux can induce eosinophilic inflammation by increasing the permeability of the esophageal mucosa to causal antigens.⁷ GERD should be

Table 1 Patient characteristics and endoscopic and histological findings in 10 patients with localized esophageal eosinophilia

Case	Age (years)	Gender	Symptom	Location of esophageal eosinophilia	Linear furrows	Concentric rings	White exudates	No. eosinophils (HPF)	Antisecretory medications at diagnosis	Gastric mucosal atrophy
1	41	Male	None	Above the EGJ	+	–	+	94	No medication	No atrophy
2	41	Male	Heartburn	Above the EGJ	+	–	+	27	No medication	No atrophy
3	35	Male	None	Above the EGJ	+	–	+	189	No medication	No atrophy
4	45	Male	None	Above the EGJ	+	+	–	18	No medication	No atrophy
5	43	Female	None	Lower esophagus	+	–	–	37	No medication	Open-type atrophy (O-1)
6	52	Male	None	Above the EGJ and middle esophagus	+	–	+	33	PPI (rabeprazole 10 mg)	No atrophy
7	44	Male	None	Above the EGJ	+	–	–	85	No medication	No atrophy
8	38	Male	dysphagia, heartburn	Above the EGJ	+	+	–	105	No medication	No atrophy
9	37	Male	None	Above the EGJ and lower esophagus	+	–	–	91	No medication	No atrophy
10	55	Female	None	Above the EGJ and lower esophagus	+	–	–	92	No medication	Closed-type atrophy (C-1)

EGJ, esophagogastric junction; HPF, high-power field; PPI, proton pump inhibitor; +, observed; –, not observed.

conceptually ruled out for definitive diagnosis of EoE,¹ but in a clinical setting, overlap between EoE and GERD has often been reported.^{8–10} In addition, it has been reported recently that a substantial number of patients with esophageal eosinophilia improve symptomatically and histologically when treated with a PPI (PPI-responsive esophageal eosinophilia), suggesting a possible association between gastric acid reflux and esophageal eosinophilia.^{11,12} In the present study, esophageal pH monitoring and PPI test were not carried out, and only two of 10 patients with localized esophageal eosinophilia had GERD symptoms. Therefore, we were unable to obtain any evidence for a positive relationship between GERD and localized esophageal eosinophilia. However, it has been reported that the squamous mucosa of the most distal esophagus is exposed to substantial acidic reflux, even in patients without evidence of conventional reflux disease.¹³ Therefore, it is conceivable that exposure to, or contact with, gastric acid above the EGJ might play a role in the development of eosinophilic inflammation localized above the EGJ, irrespective of whether GERD is evident clinically.

Endoscopic findings such as linear furrows, concentric rings or a white exudate in cases of localized esophageal eosinophilia were essentially identical to those of diffuse esophageal eosinophilia, but considerably different from those of reflux esophagitis, as represented by the Los Angeles classification.¹⁴ Also, localized esophageal eosinophilia may be confused with minimal-change esophagitis,¹⁵ which is thought to be a non-erosive form of reflux esophagitis characterized by white turbidity, redness and edematous thickening of the esophageal epithelium. It is undetermined whether localized esophageal eosinophilia is an early manifestation of typical EoE, a phenotype of GERD with dense eosinophilic infiltration, or another unknown entity. However, when such a condition is suspected on the basis of endoscopy, we think that biopsy sampling should be actively carried out whenever possible for histological confirmation and to clarify the pathogenesis of esophageal eosinophilia or EoE.

Previous Western studies have shown that the prevalence of EoE is approximately 2.2–15% in symptomatic patients with dysphagia.^{16–18} In Japan, typical EoE is considered to be very rare.¹⁹ A recent multi-institution study found only four patients with EoE among 23 346 patients undergoing upper endoscopy for a variety of reasons during one year.²⁰ Those four patients had typical EoE in terms of symptoms and endoscopy findings. Ronkainen *et al.* reported that 11 (1.1%) patients with esophageal eosinophilia, defined using a cut-off of >15 eosinophils/HPF, were found by taking random esophageal biopsy samples at 2 cm above the EGJ or at the Z-line in a general adult Swedish population.²¹ Five (45%) of the 11 patients had no troublesome reflux symptoms. Little is

Table 2 Demographic, endoscopic and histological findings in localized and diffuse esophageal eosinophilia

	Localized esophageal eosinophilia	Diffuse esophageal eosinophilia	P-value
<i>n</i>	10	23	
Age (years)	42 (35–55)	50 (32–76)	NS
Gender			
Male/female	8/2	19/4	NS
Allergic condition	7 (70%)	9 (39%)	NS
Bronchial asthma	1 (10%)	1 (4.3%)	NS
Hay fever	5 (50%)	5 (21.7%)	NS
Atopic dermatitis	1 (10%)	3 (13%)	NS
Peripheral eosinophilia (>500/ μ L)			
Presence	0 (0%)	3 (13.0%)	] NS
Absence	5 (50%)	9 (39.2%)	
Not measured	5 (50%)	11 (47.8%)	
Symptoms			
Dysphagia	1 (10%)	9 (39.1%)	NS
Heartburn	2 (20%)	7 (30.4%)	NS
Chest pain	0 (0%)	2 (8.7%)	NS
Any	2 (20%)	15 (65.2%)	<0.05 [†]
Endoscopic findings			
Linear furrows	10 (100%)	18 (78.3%)	NS
Concentric rings	2 (20%)	14 (60.9%)	NS
White exudates	4 (40%)	15 (65.2%)	NS
Histological findings			
No. esophageal biopsies	3.0 (1–5)	3.3 (1–7)	NS
No. esophageal eosinophils ($\times$ 400/HPF)	77 (18–189)	65 (16–170)	NS
Antisecretory medications at diagnosis			
PPI [‡]	1 (10%)	1 (4.3%)	NS
Gastric mucosal atrophy			
Open type	1 (10%)	5 (21%)	] NS
Closed type	1 (10%)	5 (21%)	
No atrophy	8 (80%)	13 (58%)	

[†]Fisher's exact probability test.

[‡]Rabeprazole (10 mg) was given to both patients.

HPF, high-power field; NS, not significant.

known about asymptomatic esophageal eosinophilia.²² Of the 33 patients examined in the present study, 16 had no esophageal symptoms. Thus, a substantial number of asymptomatic individuals with esophageal eosinophilia may be underdiagnosed in the general population.

Typical EoE is a chronic and relapsing disease, and can sometimes give rise to organic esophageal strictures.¹ In a follow-up study of adults with a mean follow-up time of 7.2 years, most patients had persistent symptoms and one-third needed to be treated by dilatation.²³ However, the pathogenesis and natural course of localized esophageal eosinophilia are unclear. As far as we were able to observe during the present study period, no cases of localized esophageal eosinophilia showed progression to diffuse esophageal eosinophilia. However, the prognosis of localized esophageal eosinophilia is not clear. It may progress to diffuse esophageal

eosinophilia or further to organic stricture. Therefore, we think that long-term follow up is preferable for esophageal eosinophilia irrespective of whether it is localized or diffuse.

As mentioned above, the influence of gastric acid reflux could not be evaluated in this study because esophageal pH monitoring and PPI test were not carried out. This was the most significant study limitation when considering the possible association between GERD and localized esophageal eosinophilia above the EGJ. Another limitation of this study was that the population we examined was very small, non-consecutive and heterogeneous, as the patients were recruited from several hospitals. To clarify the pathogenesis of localized esophageal eosinophilia, a larger number of patients will need to be collected and investigated. An additional limitation was that esophageal biopsy samples were obtained mainly from mucosa that appeared abnormal

endoscopically. Eosinophilic infiltration might have been detectable histologically in apparently normal mucosa if we had done random biopsies, as it has been reported previously that 10–40% of EoE cases have apparently normal endoscopic features.^{24–26} However, a recent meta-analysis of prospective studies revealed that normal endoscopic findings in EoE are uncommon,²⁷ suggesting that abnormal features might be detected frequently if exhaustive and careful endoscopic observation is carried out.

In summary, our study findings indicate that esophageal eosinophilia can be localized in a small area, especially just above the EGJ. Gastric acid reflux or contact may influence this condition in addition to its allergic pathogenesis.

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CONFLICT OF INTERESTS

AUTHORS DECLARE NO conflict of interests for this article.

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