Clinical Features of Esophageal Eosinophilia According to Endoscopic Phenotypes

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Abstract:
Objective Esophageal eosinophilia (EE), a histological hallmark of eosinophilic esophagitis, is classified into two endoscopic phenotypes: localized and diffuse EE. Our aim was to determine the prevalence of EE localized in the lower esophagus and to describe its clinical features in comparison with diffuse EE.

Methods Data from 81 consecutive patients with EE were retrospectively investigated. EE was histologically defined as ≥15 eosinophils per high-power field. Based on the endoscopic appearance with a histological assessment, EE was classified as either diffuse or localized type. We compared the clinical features, including the medical treatment and natural course, between the two types.

Results Of the 81 patients, 52 (64.2%) had diffuse EE, and 29 (35.8%) had localized EE. Among men patients, localized EE was significantly more common than diffuse EE. In localized EE, dysphagia and food impaction were less prevalent, and the presence of rings was significantly less common than in diffuse EE. Acid-suppressive therapy was administered to only 3 of the 29 patients with localized EE. In asymptomatic patients, especially those with localized EE, endoscopic abnormalities did not worsen but rather improved in some findings, such as with regard to furrows or exudate, during the natural course of three years without medical treatment.

Conclusion Localized EE has a strong predilection for men patients and accounted for more than one third of all cases of EE. This condition appears to be less symptomatic and necessitates milder medical treatment than diffuse EE and might not worsen progressively.

Key words: eosinophilic esophagitis, esophageal eosinophilia, endoscopic phenotype, localized esophageal eosinophilia, diffuse esophageal eosinophilia

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Introduction

Eosinophilic esophagitis (EoE) is a Th2 cell-immune-mediated inflammatory disease characterized by symptoms of esophageal dysfunction and prominent esophageal eosinophilia (EE) (1). Since 1990, EoE has emerged as a major cause of dysphagia and food impaction, especially among Western populations (2, 3). A large number of studies have elucidated the epidemiological features, diagnosis, molecular mechanisms, medical treatments, and prognosis of EoE to uncover the pathogenesis of this emerging disease; however, many aspects remain unclear (4). Furthermore, EoE is of considerable concern as an emerging non-acid-related esophagitis in Asia, including Japan, as evidenced by a recent increase in reported cases (5-9).

Several endoscopic findings, including exudate, rings, edema, furrows, and strictures, have been reported to be characteristics of EoE (10). A meta-analysis by Kim et al. showed that at least one of these abnormalities was endo-

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symptoms or periodic checkups for gastrointestinal malig-
examination performed for various upper gastrointestinal
2018.

Shinoda General Hospital) between July 2011 and July
33 at JR Sendai Hospital, and 23 at
who received a diagnosis of EE at 1 of 3 study hospitals in

tive patients with a diagnosis of EE.

Among all cases of EE is available, and its clinical features,
formation about the proportion of cases of localized EE
was noted in a small area of the lower esophagus (12). This group
also found that the localized type of EE was associated with
significantly fewer esophageal symptoms than was the diff-
use type of EE, but that study consisted of nonconsecu-
tively enrolled patients and included only 10 patients with
localized EE.

Recently, Sawada et al. reported high rates of responsive-
ness to therapy with proton pump inhibitors (PPIs) in symp-
tomatic patients with localized EE (13). However, little in-
formation about the proportion of cases of localized EE
among all cases of EE is available, and its clinical features,
including the practical medical treatment and natural course,
compared with those of diffuse EE are unclear.

Given the above, we compared the clinical features of lo-
calized EE with those of diffuse EE in a cohort of consecu-
tive patients with a diagnosis of EE.

Methods

This retrospective study included 81 consecutive patients
who received a diagnosis of EE at 1 of 3 study hospitals in
Yamagata and Miyagi Prefectures, Japan (25 at Yamagata
University Hospital, 33 at JR Sendai Hospital, and 23 at
Shinoda General Hospital) between July 2011 and July
2018.

The EE diagnosis was based on findings of an endoscopic
examination performed for various upper gastrointestinal
symptoms or periodic checkups for gastrointestinal mali-
gnancy. EE was histologically defined as the presence of ≥15
eosinophils per high-power field (HPF). The endoscopic
phenotype was defined according to the endoscopic appear-
ance, with supporting findings of the histological assess-
ment, in reference to previous report as follows (12): The
diffuse type was defined as a widespread area of EE involv-
ing one or more of three locations: upper, middle, and lower
esophagus (Fig. 1). The localized type was defined as a
small area of EE localized within 1 to 2 cm of the lower
esophagus (Fig. 1). At least one biopsy sample was obtained
from normal-appearing mucosa above the affected area in
each patient, and insignificant eosinophilic accumulation (≤5
eosinophils/HPF) was confirmed histologically.

Focal EE that was far away from the lower end of the
esophagus was included in the “localized type” in our previ-
ous report (12), but in the present study, it was defined as
patchy type and incorporated into the diffuse type in order
to focus on the localized type at the lower end of the
esophagus (Fig. 1).

The five endoscopic findings of EoE—rings, furrows exu-
date, edema (decreased vascularity), and stricture—were as-
essed qualitatively (for their absence or presence). In addi-
tion, they were originally and semiquantitatively scored as
follows in reference to a previous report (10): For rings, fur-
rows, and edematous mucosa was interspersed with exudate, furrows, or both, with an appearance re-
sembling skip lesions in the esophagus and intervening normal-appearing mucosa. (d) The propor-
tions of these three endoscopic phenotypes.

Figure 1. The representative endoscopic images of diffuse EE (EE; a1 and a2), localized EE (b1 and
b2), and patchy-type EE (c1 and c2); The proximal esophagus (a1, b1, and c1) and distal esophagus
(a2, b2, c2) are shown. In patients with diffuse EE (a1 and a2), furrows, rings, and exudate were found
in almost all areas of the esophagus. In patients with localized EE (b1 and b2), furrows, rings, and
exudate were observed only in the lower end of the esophagus. In patients with patchy-type EE (c1
and c2), edematous mucosa was interspersed with exudate, furrows, or both, with an appearance re-
sembling skip lesions in the esophagus and intervening normal-appearing mucosa. (d) The propor-
tions of these three endoscopic phenotypes.
Endoscopic examinations at the three hospitals were performed by endoscopists familiar with EoE and certified by the Japanese Gastrointestinal Endoscopy Society (Y.A., T.K., and Y.S. in Yamagata University Hospital; Y.A. in Shinoda General Hospital; and R.K., S.U., and G.K. in JR Sendai Hospital). Furthermore, all endoscopic images were ultimately subjected to a detailed review and assessed by two endoscopists (K.T. and Y.A.). When they disagreed on the assessment, agreement was sought through discussion.

Medical treatments administered to patients with symptomatic EE, including proton pump inhibitors (PPIs), potassium-competitive acid blockers, and topical corticosteroids, were reviewed by assessing medical charts. Symptoms, abnormalities, and eosinophilic inflammation after the medical treatment documented in the records, including the endoscopy reports and pathological reports, were also reviewed. The disappearance of symptoms and eosinophilic infiltration, with ≤5 eosinophils/HPF after the standard dose of PPIs for at least eight weeks (or potassium-competitive acid blocker for at least four weeks), according to PPI treatment for erosive esophagitis, were assessed as clinical and histological remission, respectively (16, 17).

This study was approved by the ethics committees of the participating hospitals and conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all patients before participation in the study.

Statistical analyses

Data are expressed as medians with ranges or as numbers with percentages. For comparisons between patients with diffuse and localized EE, continuous variables were analyzed with Wilcoxon’s rank sum test or Wilcoxon’s signed rank test, and categorical variables were analyzed with Fisher’s exact probability tests. All statistical analyses were performed with the JMP® software program, version 14.1.0 (SAS Institute, Cary, NC, USA). A P value of <0.05 was considered statistically significant.

Results

Of the 81 patients with EE (median age, 49; range, 18 to 77 years), 69 were men, and 12 were women: 49 patients (60.5%) were classified as having diffuse EE, and 29 (35.8%) were classified as having localized EE. The remaining 3 patients (3.7%) exhibited focal edematous mucosa with exudate, furrows, or both, which were observed as skip lesions, away from the lower end of the esophagus. We designated these three patients as patchy type, which was promptly included as diffuse EE in the subsequent analyses (Fig. 1).

Table 1 summarizes the characteristics of the 81 patients. All but 1 patient with localized EE were men, which was significantly different from the gender ratio among patients with diffuse EE (p=0.0476). The frequencies of diagnostic opportunities (gastrointestinal screening, including periodic checkups or endoscopic examinations for any gastrointestinal symptoms), upper gastrointestinal symptoms, and PPI use at the time of the first diagnosis were not significantly different between the two groups. Bronchial asthma was significantly more common in the diffuse type (13.5%) than in the localized type (0%; p=0.046). Rings were significantly more prevalent among patients with diffuse EE than among those with localized EE (p=0.0004), whereas the remaining endoscopic findings were present to comparable degrees in both groups. The endoscopic score for rings and the total endoscopic score were significantly higher for patients with diffuse EE than for those with localized EE (for rings, p=0.0001; for total endoscopic score, p=0.018). The prevalence of hiatal hernia, which was similar in the two groups, was evaluated only in patients who underwent endoscopy with a regular transoral endoscope. The histological grade of EE did not differ markedly between the two groups.

Next, we reviewed the medical treatment documented on medical charts. As first-line therapy, PPIs were administered orally for at least 8 weeks to 17 of 52 patients with diffuse EE but to only 2 of 29 patients with localized EE. In addition, two patients (one in the diffuse group and one in the localized group) took the standard dose of potassium-competitive acid blocker for four weeks because of concomitant peptic ulcer or severe heartburn based on the clinical judgment of the attending physician. In total, acid-suppressive therapy was performed in 18 of 52 diffuse patients (34.6%) and 3 of 29 localized EE (10.3%).

With acid-suppressive therapy, 11 of the 18 patients with diffuse EE achieved clinical remission, and 6 of those 11 patients were judged to have achieved clinical and histological remission. All three patients with localized EE achieved clinical remission, and two of the three achieved histological remission.

The endoscopic and histological findings before and after acid-suppressive therapy according to the two endoscopic phenotypes are shown in Table 2. The prevalence of furrows and exudate decreased significantly after acid-suppressive therapy in the diffuse type (p=0.0001, p=0.0377, respectively). The furrow score, total endoscopic score, and number of histological esophageal eosinophilia in the diffuse type were also decreased significantly after the therapy (p=0.0005, p=0.0012, p=0.002, respectively). In contrast, the endoscopic and histological findings tended to improve in the localized type after the therapy, although not to a significant degree. Topical steroid therapy with a liquid budesonide formulation was applied to none of the patients with localized EE and to five patients with diffuse EE who were unresponsive to PPI therapy. All 5 of those patients achieved clinical and histological remission within 8-12 weeks after the therapy.

Next, we compared the patients according to the presence or absence of esophageal symptoms. There were no significant differences in the age, gender, allergic diseases, or endoscopic and histological findings between the symptomatic and asymptomatic patients (Table 3). To further evaluate the pathogenesis of the asymptomatic patients, we reviewed the
Table 1. Baseline Characteristics of Patients with Diffuse- and Localized-type Esophageal Eosinophilia.

|                                | Diffuse EE | Localized EE | p value |
|--------------------------------|------------|--------------|---------|
| n                              | 52         | 29           | -       |
| median age (range, years)      | 48.5 (18-74)| 49 (33-77)   | ns      |
| gender                         |            |              |         |
| men (%)                        | 41 (78.8)  | 28 (96.6)*   | P=0.0476* |
| allergic diseases (%)          |            |              |         |
| bronchial asthma               | 7 (13.5)   | 0            | P=0.0460* |
| allergic rhinitis              | 20 (37.1)  | 11 (37.9)    | ns      |
| atopic dermatitis              | 3 (5.7)    | 2 (6.9)      | ns      |
| any                            | 26 (50.0)  | 13 (44.8)    | ns      |
| diagnostic opportunities       |            |              |         |
| GI screening (%)               | 43 (82.7)  | 23 (79.3)    | ns      |
| GI symptoms (%)                | 3 (5.8)    | 4 (13.8)     | ns      |
| others (%)                     | 6 (11.5)   | 2 (6.9)      | ns      |
| any upper GI symptoms          | 19 (36.5)  | 7 (24.1)     | ns      |
| dysphagia (%)                  | 11 (21.2)  | 2 (6.9)      | ns      |
| food impaction (%)             | 6 (11.5)   | 0 (0)        | ns      |
| heartburn (%)                  | 16 (30.7)  | 7 (24.1)     | ns      |
| others (%)                     | 4 (7.7)    | 1 (3.4)      | ns      |
| PPI use at the first diagnosis(%)| 2 (3.8) | 1 (3.4%)     | ns      |
| History of esophageal dilatation (%) | 0     | 0            | ns      |
| prevalence of endoscopic findings |        |              |         |
| rings (%)                      | 36 (69.2)  | 8 (27.6)*    | p=0.0004* |
| furrows (%)                    | 42 (80.7)  | 27 (93.1)    | ns      |
| exudate (%)                    | 40 (76.9)  | 23 (79.3)    | ns      |
| edema (decreased vascularity) (%) | 52 (100) | 29 (100)     | ns      |
| stricture (%)                  | 1 (1.9)    | 0 (0)        | ns      |
| endoscopic score (median, range) |        |              |         |
| rings                          | 1 (0-2)    | 0 (0-1)      | p=0.0001** |
| furrows                        | 2 (0-2)    | 2 (0-2)      | ns      |
| exudate                        | 1 (0-1)    | 1 (0-1)      | ns      |
| edema (decreased vascularity)  | 1 (1-1)    | 1 (1-1)      | ns      |
| stricture                      | 0 (0-1)    | 0 (0-0)      | ns      |
| total                          | 4 (1-6)    | 3 (2-5)      | p=0.018** |
| erosive esophagitis(%)         | 6 (11.5)   | 1 (3.4)      | ns      |
| hiatal hernia                  | 7/42*** (16.7) | 4/22*** (18.2) | ns      |
| number of esophageal eosinophil (HPF) (median, range) | 62 (17-258) | 46 (16-162) | ns      |
| abnormal-appearing area        | -          | 0 (0-12)     | -       |
| normal-appearing mucosa        | -          |              | -       |

*Fisher’s exact probability test  
**Wilcoxon’s rank sum test  
***Ten diffuse EE and seven localized EE patients who were assessed using nasal endoscopy with a small caliber were excluded.

EE: esophageal eosinophilia

endoscopic findings and rates of EE among asymptomatic patients who had long-term follow-up. Thirty-seven of 52 (71%) patients with diffuse EE and 16 of 29 (55%) patients with localized EE underwent follow-up EGD after the initial diagnosis of EE. Since very few patients had a follow-up of more than five years, we considered a follow-up of more than three years as “long-term follow-up” in this study and analyzed the natural course of asymptomatic patients. When we compared the first and last endoscopy findings, none of the asymptomatic EE patients had progressed to symptomatic EE, at least in this study period. In 5 of 14 patients with the diffuse type and 1 of 7 patients with the localized type, PPIs were administered at the last follow-up endoscopy to maintain endoscopic and histological remission in the absence of esophageal symptoms. In the diffuse type, endoscopic exudate scores were significantly decreased at the last follow-up endoscopy compared to the first session (p=0.0313). In the localized type, the prevalence of furrows and total endoscopic scores were significantly decreased at the last follow-up endoscopy compared to the first session (p=0.0291, p=0.0156, respectively; Table 4). After excluding from both groups a total of 6 PPI users at the last follow-up endoscopy, the decreased total endoscopic score at the last endoscopy in the localized group remained significant (p=
Discussion

In this study of consecutively recruited patients with EE at three hospitals in Japan, we found that one-third of the patients exhibited localized involvement of the lower esophagus. To our knowledge, this is a novel finding. Since asymptomatic EE patients in this studied population were more common, irrespective of endoscopic phenotypes, than symptomatic EE patients, we investigated their clinical features, including the medical treatment and long-term prognosis, according to the presence or absence of esophageal symptoms. We did not detect any pathophysiological differences, including in endoscopic phenotypes, between symptomatic and asymptomatic EE patients; however, we noted that asymptomatic EE patients were unlikely to progress to typical EE, at least during the median follow-up of four or five years in this study.

Furthermore, we found that localized EE may spontaneously remit during its natural course. To our knowledge, this was another novel finding of this study. Patients with EoE diagnosed in Western countries, most of whom are symptomatic and go undiagnosed for a long period of time, experience the complication of esophageal stricture as a consequence of chronic eosinophilic inflammation unless they have undergone appropriate treatment (18-20). Since asymptomatic patients with EE are commonly encountered during screening endoscopy for health checkups in Japan (9), our finding that their conditions do not seem to worsen during the natural course of several years may be useful information in the management of EE in the clinical setting.

Asymptomatic EE is not diagnosed as EoE according to the current diagnostic criteria for EoE (1, 4). In Japan, upper gastrointestinal screening by endoscopy has been widely performed in public health care checkup programs and general clinical practice for the early detection of upper gastrointestinal malignancy; it enables the diagnosis of EE in patients with minimal or mild symptoms (9, 21). This is concordant with our findings, which revealed that in 80% of the patients with EE, regardless of the endoscopic phenotype, the disease was diagnosed through gastrointestinal screening. Because of the difficulty in adequately assessing subjective symptoms in EoE, it may be expedient in Japanese clinical practice for EE without esophageal symptoms to instead be
Table 3. Baseline Characteristics of Patients with Asymptomatic and Symptomatic EE.

|                        | asymptomatic EE | symptomatic EE | p value |
|------------------------|-----------------|----------------|---------|
| n                      | 54              | 27             |         |
| median age (range, years) | 49 (33-74)      | 48 (18-77)     | ns      |
| men (%)                | 49 (90.7)       | 20 (74.0)      | ns      |
| allergic diseases (%)   |                 |                |         |
| bronchial asthma        | 3 (5.6)         | 4 (14.8)       | ns      |
| allergic rhinitis       | 20 (37.0)       | 11 (40.7)      | ns      |
| atopic dermatitis,      | 3 (5.6)         | 2 (7.4)        | ns      |
| any                     | 27 (50.0)       | 12 (44.4)      | ns      |
| diagnostic opportunities |                |                |         |
| EGD for health checkup (%) | 47 (87.0)     | 19 (70.4)      | ns      |
| EGD for GI symptoms (%) | 1 (1.9)*        | 6 (22.2)       | p=0.0049*** |
| others (%)              | 6 (11.1)        | 2 (7.4)        | ns      |
| upper GI symptoms       |                |                |         |
| dysphagia (%)           | -               | 12 (22.2)      | -       |
| food Impaction (%)      | -               | 5 (9.3)        | -       |
| heartburn (%)           | -               | 20 (37.0)      | -       |
| others (%)              | 1 (1.9)*        | 3 (11.1)       | -       |
| PPI use at the first diagnosis (%) | 1 (1.9)    | 1 (3.7)        | ns      |
| past history of esophageal dilatation |        |                |         |
| endoscopic phenotypes   |                |                |         |
| diffuse (%)             | 29 (53.7)       | 20 (74.1)      | ns      |
| localized (%)           | 22 (40.7)       | 7 (25.9)       | ns      |
| patchy (%)              | 3 (5.6)         | 0              | ns      |
| prevalence of endoscopic findings |          |                |         |
| rings (%)               | 28 (51.6)       | 16 (59.3)      | ns      |
| furrows (%)             | 45 (83.3)       | 24 (88.8)      | ns      |
| exudate (%)             | 43 (79.6)       | 20 (74.1)      | ns      |
| edema (decreased vascularity) (%) | 54 (100)      | 27 (100)       | ns      |
| stricture (%)           | 0 (0)           | 1 (3.7)        | ns      |
| endoscopic score (median, range) |          |                |         |
| rings                   | 1 (0-2)         | 1 (0-2)        | ns      |
| furrows                 | 2 (0-2)         | 2 (0-2)        | ns      |
| exudate                 | 1 (0-2)         | 1 (0-1)        | ns      |
| edema (decreased vascularity) | 1 (1-1)       | 1 (1-1)        | ns      |
| stricture               | 0 (0-0)         | 0 (0-1)        | ns      |
| total                   | 4 (1-7)         | 4 (2-6)        | ns      |
| erosive esophagitis (%) | 6 (11.1)        | 1 (1.2)        | ns      |
| hiatal hernia           | 6/43*** (14.0)  | 5/21*** (23.8) | ns      |
| number of esophageal eosinophilia/HPF (median, range) | 57 (18-209) | 46 (16-258) | ns      |

*This patient had nausea.
**Fisher’s exact probability test
***Eleven asymptomatic EE and 6 symptomatic EE patients who were assessed using nasal endoscopy with a small caliber were excluded.
EE: esophageal eosinophilia, EGD: esophagogastroduodenoscopy, PPI: proton pump inhibitor

managed as “asymptomatic EoE” to further clarify the pathogenesis of EoE (22). However, a systematic review of EoE in Asian populations revealed that dysphagia was a major symptom experienced by 40% of affected patients and that food impaction was experienced by only 4% of the patients (23). In our present study, dysphagia was present in 11 (21.2%) patients with diffuse EE and 2 (6.9%) patients with localized EE. Food impaction and esophageal stricture were also found in only 6 (11.5%) and 1 (1.9%) of the 52 patients with diffuse EE, respectively. None of the patients had undergone esophageal dilatation. The similarities in the pathogenic mechanism underlying EoE in Japan and Western countries were shown by a transcriptomic study (24). The cause of milder disease severity observed in Japanese patients than in Western patients, while unclear, might involve environmental factors, such as dietary habits, and early life factors (25).

Given the spatial extent of eosinophilic inflammation in the esophageal lumen, it is logical for dysphagia or food impaction to be milder in the localized type than in the diffuse
patients with localized EE than in those with diffuse EE, but
dysphagia and food impaction tended to be less common in
type. In our present study as well in our previous report,
this finding was not statistically significant. Sawada et al. re-
ported that asymptomatic patients were more common in the
localized group (42%) than in the diffuse group (7%), with

Table 4. Endoscopic and Histological Findings at the First and Last Endoscopy Session in Asymptomatic EE with Long-term
Follow up of More than Three Years.

|                      | Diffuse EE          |        | P value | Diffuse EE          |        | P value |
|----------------------|---------------------|--------|---------|---------------------|--------|---------|
| n                    | 14                  | 14     | -       | 7                   | 7      | -       |
| mean age at the first diagnosis (range, years) | 52 (37-74)         | -      | -       | 52 (44-74)         | -      | -       |
| mean number of follow-up endoscopy | 5 (3-7)            | 4 (3-6) |         |                      |        |         |
| median follow up period (range, months) | 61 (36-82)         | 49 (39-72) |         |                      |        |         |
| progression to symptomatic EE | -                  | 0      | -       | -                  | 0      | -       |
| PPI users (%) | 1 (7.1)            | 5 (35.7) | ns      | 0                  | 1 (14.3%) | ns      |
| prevalence of endoscopic findings |                      |        |         |                      |        |         |
| rings (%) | 8 (57.1)            | 8 (57.1) | ns      | 2 (28.6)           | 1 (14.3) | ns      |
| furrows (%) | 10 (71.4)          | 7 (50.0) | ns      | 6 (85.7)           | 1 (14.3)* | p=0.0291 |
| exudate (%) | 12 (85.6)          | 8 (57.1) | ns      | 3 (42.9)           | 1 (14.3) | ns      |
| edema (decreased vascularity) (%) | 14 (100)         | 12 (85.7) | ns      | 7 (100)            | 6 (85.7) | ns      |
| stricture (%) | 0 (100)           | 0 (100) | ns      | 0                  | 0       | ns      |
| endoscopic score (median, range) |                      |        |         |                      |        |         |
| rings | 1 (0-2)             | 1 (0-2) | ns      | 0 (0-1)            | 0 (0-1) | ns      |
| furrows | 1.5 (0-2)          | 0.5 (0,2) | ns      | 2 (0-2)           | 0 (0-2) | ns      |
| exudate | 1 (0-2)            | 1 (0-1) | p=0.0313** | 0 (0-1)       | 0 (0-1) | ns      |
| Edema (decreased vascularity) | 1 (1-1)          | 1 (0-1) | ns      | 1 (1-1)           | 0 (0-1) | ns      |
| stricture | 0 (0-0)           | 0 (0-0) | ns      | 0 (0-0)           | 0 (0-0) | ns      |
| total score | 4 (1-7)          | 3 (0-7) | ns      | 3 (2-5)           | 1 (0-4)** | p=0.0156 |
| number of esophageal eosinophilia (/HPF) (median, range) | 57.5 (18-118) | 76 (0-110)*** | ns | 54 (33-162) | 10 (0-46)*** | ns |

*Fisher’s exact probability test
**Wilcoxon’s signed rank test
***Esophageal biopsies were not obtained from 5 of 14 diffuse and 2 of 7 localized patients in the last endoscopy.
EE: esophageal eosinophilia, EGD: esophagogastroduodenoscopy, PPI: proton pump inhibitor

Figure 2. Chronological changes in the total endoscopic score between the first and last endoscopy session in asymptomatic patients who had a long-term follow-up of more than three years. After excluding from both groups a total of 6 PPI users at the last follow-up endoscopy session, the decreased total endoscopic score of the last endoscopy remained significant in the localized group but not in the diffuse group (p=0.0313, Wilcoxon’s signed rank test).
The manifestation of erosive esophagitis may be masked by the normalities that can occur locally; consequently, endoscopic study. However, when certain causal antigens come into one with grade A of 29 patients with localized EE in this study. In Table 1, concomitant erosive esophagitis was found only in 10% of the patients with localized EE. According to our review of medical charts, aggressive medical treatment seems to be unnecessary for localized EE in clinical practice, as the localized inflammation induces fewer symptoms (13). Finally, our findings that significant symptoms and endoscopic progression were less likely to occur in asymptomatic EE patients for at least several years were based on a retrospective observation of a small number of patients. This may imply transient eosinophilic inflammation in localized EE. A large prospective study is necessary to determine whether localized or asymptomatic EE patients progress to typical EoE.

In summary, we found that one-third of the patients with EE displayed localized involvement of the lower esophagus; patients with localized EE were predominantly men, and localized EE necessitated less active medical treatment than did diffuse EE. Localized EE might not worsen progressively, at least during the short-term period of a few years.

The authors state that they have no Conflict of Interest (COI).

References

1. Liacouras CA, Furta GT, Hirano I, et al. Eosinophilic esophagitis: updated consensus recommendations for children and adults. J Allergy Clin Immunol 128: 3-20, 2011.
2. Prasad GA, Alexander JA, Schleck CD, et al. Epidemiology of eosinophilic esophagitis over three decades in Olmsted County,
18. Lipka S, Kumar A, Richter JE. Impact of diagnostic delay and other risk factors on eosinophilic esophagitis phenotype and esophageal diameter. J Clin Gastroenterol 50: 134-140, 2016.
19. Koutlas NT, Dellon ES. Progression from an inflammatory to a fibrostenotic phenotype in eosinophilic esophagitis. Case Rep Gastroenterol 11: 382-388, 2017.
20. Sato H, Honma T, Nozawa Y, et al. Eosinophilic esophagitis in Japanese patients: A mild and slow-progressing disorder. PLoS One 13: e0206621, 2018.
21. El-Matary W. Natural history of eosinophilic esophagitis in asymptomatic patients. Gastroenterology 146: 1426, 2014.
22. Kimura I, Toyama T, Hara M, et al. Comparison of gene expression profiles in eosinophilic esophagitis (EoE) between Japan and Western countries. Allergol Int 64: 260-265, 2015.
23. Ishinuma N, Shimura S, Jiao D, et al. Clinical features of eosinophilic esophagitis: Differences between Asian and Western populations. J Gastroenterol Hepatol 30: 71-77, 2015.
24. Ishinuma N, Sumi S, Okada M, et al. Is Asymptomatic Esophageal Eosinophilia the Same Disease Entity as Eosinophilic Esophagitis?. Clin Gastroenterol Hepatol 17: 1405-1407, 2019.
25. Remedios M, Campbell C, Jones DM, Kerlin P. Eosinophilic esophagitis in adults: Clinical, endoscopic, histologic findings, and response to treatment with fluticasone propionate. Gastroent Test Endosc 63: 3-12, 2006.
26. Molina-Infante J, Ferrando-Lamana I, Ripoll C, et al. Esophageal eosinophilic infiltration responds to proton pump inhibition in most adults. Clin Gastroenterol Hepatol 9: 110-117, 2011.
27. Fletcher J, Wirz A, Henry E, McColl KEL. Studies of acid exposure immediately above the gastro-oesophageal squamocolumnar junction: evidence of short segment reflux. Gut 53: 168-173, 2004.
28. Furukawa N, Iwakiri R, Koyama T, et al. Proportion of reflux eosinophilic esophagitis in 6010 Japanese adults: Prospective evaluation by endoscopy. J Gastroenterol 34: 441-444, 1999.
29. Ito M, Hara M, Fujisawa Y, et al. Proportion of reflux eosinophilic esophagitis in 6010 Japanese adults: Prospective evaluation by endoscopy. J Gastroenterol 34: 441-444, 1999.
30. Shimazu T, Matsui T, Furukawa K, et al. A prospective study of the prevalence of gastroesophageal reflux disease and confounding factors. J Gastroenterol 40: 866-872, 2005.
31. Spechler SJ, Genta RM, Souza RF. Thoughts on the complex relationship between gastroesophageal reflux disease and eosinophilic esophagitis. Am J Gastroenterol 102: 1301-1306, 2007.
32. Izumi D, Ishinuma N, Okada M, et al. Poor inter-observer agreement on the endoscopic diagnosis of eosinophilic esophagitis among Japanese endoscopists. Esophagus 14: 309-316, 2017.
33. Peery AF, Cao H, Dominik R, et al. Variable reliability of endoscopic findings with white-light and narrow-band imaging for patients with suspected eosinophilic esophagitis. Clin Gastroenterol Hepatol 9: 475-480, 2011.
34. Fukushima Y, Hashimoto A, Umemura R, et al. Optimal biopsy protocol to evaluate histological effectiveness of proton pump inhibitor therapy in patients with eosinophilic esophagitis. Digestion 100: 64-71, 2019.