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ORIGINAL ARTICLE

Barrett's esophagus is negatively associated with eosinophilic esophagitis in Japanese subjects

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Abstract

Background Although both eosinophilic esophagitis (EoE) and Barrett's esophagus (BE) are considered to be associated with T helper (Th) 2-mediated immune responses, the association between EoE and BE is unclear. We investigated the clinical relationship between EoE and BE.

Methods We conducted a single-center retrospective observational study. The study included 95 patients with EoE and randomly selected age- and sex-matched controls who underwent esophagogastroduodenoscopy during a medical health check-up at Osaka City University in a ratio of 1:2 for comparison. We compared the clinical characteristics and the prevalence rate of BE, reflux esophagitis (RE), hiatal hernia, and atrophic gastritis between EoE patients and controls by univariate analysis. Furthermore, we performed multivariate logistic regression analysis to investigate the association of these factors with EoE.

Results On univariate analysis, the prevalence rate of BE was significantly lower in patients with EoE than in controls (2.1% vs. 13.2%; $p=0.00528$). In contrast, the prevalence rate of RE was higher in EoE patients than in controls, but it was not statistically significant (absence and Grades A, B, and C: 74.7%, 18.9%, 5.3%, and 1.1% vs. 83.7%, 12.6%, 3.7%, and 0%; $p=0.193$, respectively). Multivariate analysis showed that BE was negatively associated with EoE (odds ratio: 0.132; 95% confidence interval: 0.0302–0.573; $p=0.00686$).

Conclusions BE is negatively associated with EoE in Japanese subjects. The mechanism behind the inverse relationship between EoE and BE should be examined.

Keywords Eosinophilic esophagitis · Barrett's esophagus · Peptic esophagitis · Esophagus · Eosinophils

Introduction

Eosinophilic esophagitis (EoE) is a chronic esophageal inflammatory disease, clinically characterized by symptoms of esophageal dysfunction, and histologically characterized by dense infiltration of eosinophils and related chronic inflammation in the epithelial layers of the esophageal mucosa on esophageal biopsy [1, 2]. Although EoE has not been associated with an increased risk of mortality or cancer, the chronic progressive nature of the disease has a negative impact on patients' quality of life [3]. Japanese studies have shown that the prevalence of EoE was between 14.7 and 17.1 per 100,000 patients [4, 5]. In the pathogenesis of EoE, the inflammation is triggered by various foods and possibly by environmental allergens [6]. EoE was considered as a T helper (Th) 2-mediated disease acting via thymic stromal lymphopoietin (TSLP) production in the esophageal epithelium in eosinophil-related inflammation [7].

Barrett's esophagus (BE) is an acquired condition in which the squamous epithelium is replaced by the columnar-lined mucosa with intestinal metaplasia. Compared with the pro-inflammatory nature of reflux esophagitis (RE), BE is characterized by a distinct Th2-predominant cytokine profile in humans [8]. We previously showed that levels of Th2 cytokines such as IL-4, IL-10, and IL-13 were significantly increased in BE compared with non-BE [9]. Although both EoE and BE are related to Th2-mediated immune responses, the association between EoE and BE is unclear. Therefore,

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we investigated the clinical relationship between EoE and BE in this study.

Methods

Study design and participants

We conducted a single-center retrospective observational study. Between January 2015 and September 2017, we enrolled EoE subjects who visited the Osaka City University Hospital and non-EoE control subjects who received comprehensive medical examination at Osaka City University Hospital Advanced Medical Center for Preventive Medicine (MedCity21) in this study. We clinicopathologically diagnosed EoE by the presence of symptoms related to esophageal dysfunction and esophageal biopsy demonstrating ≥ 15 eosinophils per high-power field (HPF) according to the United European Gastroenterology Guideline in 2017 [10]. In patients with EoE, mucosal eosinophilia was restricted to the esophagus. The subjects who did not have any symptoms and typical endoscopic findings for EoE among those who underwent medical health check-ups including esophagogastroduodenoscopy (EGD) were considered as controls. We considered typical endoscopic findings as follows: longitudinal furrows, esophageal rings, white exudates or plaques, and mucosal edema. We selected patients with EoE and randomly selected age- and sex-matched controls in a ratio of 1:2 for the comparison. Two matched controls were randomly selected for each of EoE patients from the pool of individuals who underwent medical health check-ups including EGD. Matching was based on sex and exact age. The following subjects were excluded from the study: subjects aged < 18 years, those with poor study results with gastric residue on EGD, patients who were diagnosed with upper gastrointestinal cancer, patients who underwent gastrointestinal surgery, patients who had current intake of proton pump inhibitors (PPIs), and EoE patients who did not undergo matching with controls. We collected data including age, height, body weight, body mass index (BMI), sex, current smoking status (presence/absence), and current alcohol consumption status (presence/absence) from the medical records.

The study protocol was approved by the Ethics Committee of the Osaka City University Graduate School of Medicine and it was performed in accordance with the principles of the Helsinki Declaration.

Endoscopic examination

Well-trained endoscopists board-licensed by the Japan Gastroenterological Endoscopy Society performed the endoscopic examinations. Two expert endoscopists (S.T. and F.T.) checked the photographs taken by the endoscopists. We observed endoscopic findings including BE (presence/absence), RE (absence and Grade A, B, C, or D), hiatal hernia (presence/absence), and atrophic gastritis (presence/absence). The esophagogastric junction (EGJ) was defined as the most distal ends of the palisade longitudinal vessels in the esophagus. The squamocolumnar junction (SCJ) was defined as the border of the esophageal squamous epithelium and gastric columnar epithelium. The gap between SCJ and EGJ was diagnosed as endoscopically observed BE in Japan [11]. A lining measuring less than 10 mm, reported as an 'ultrashort segment' of BE [12], was not considered to indicate BE in this study, because its diagnostic criteria were vague and there might be a high degree of inter-observer variation. A typical endoscopic image of BE is shown in Fig. 1. There were 4 subjects in the control group who had history of BE in the previous endoscopies. RE was defined according to the Los Angeles classification (Grades A–D) [13]. The presence of hiatal hernia was characterized by the proximal dislocation of the EGJ > 20 mm above the diaphragmatic indentation. Atrophic gastritis was diagnosed based on the endoscopic extent of atrophic mucosa, which was graded according to the Kimura–Takemoto classification from C-1 to O-3 [14]. Subjects with atrophic mucosa graded as C-2, C-3, O-1, O-2, and O-3 were described as positive for atrophic gastritis.

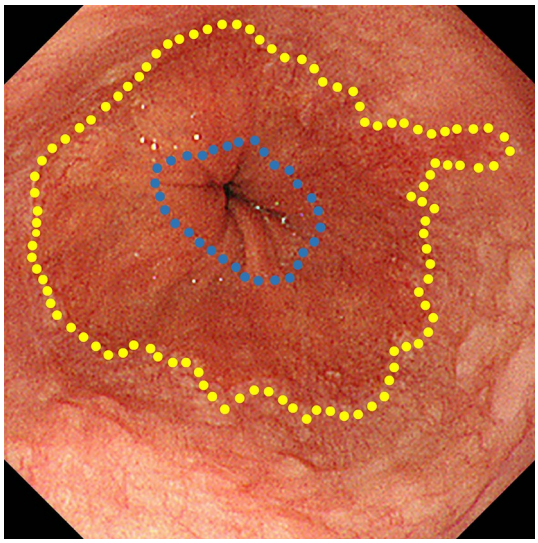

Fig. 1 Typical image of Barrett's esophagus (BE). The esophagogastric junction (EGJ) is the most distal end of the palisading longitudinal esophagus vessels. The squamocolumnar junction (SCJ) is the border of esophageal squamous epithelium and gastric columnar epithelium. The area surrounded in blue dots is EGJ and that surrounded in yellow dots is SCJ. The gap between SCJ and EGJ is diagnosed as endoscopically observed BE

Outcome measurement

We compared the clinical characteristics and endoscopic findings between EoE patients and controls. The endpoint of this study was to clarify the association between EoE and BE.

Statistical analysis

All variables were reported as mean ± standard deviation or numbers (percentage). Pearson's χ^2 test was used to compare categorical variables. The continuous variables were evaluated by unpaired *t* test. A multivariate analysis for categorical variables was performed using logistic regression. Furthermore, we performed a multivariate logistic regression analysis to investigate the association of these factors with EoE and expressed it as odds ratio (OR) with 95% confidence interval (CI). A *p* value less than 0.05 was considered significant. Variables with *p* value < 0.200 on univariate analyses were included in multivariate analysis. The Cohen's kappa analysis of agreement was used to evaluate the reliability of endoscopic findings of BE between two estimators. All statistical analyses were performed using EZR (Saitama Medical Center, Jichi Medical University), which is a graphical user interface for R (The R Foundation for Statistical Computing, version 2.13.0) [15].

Results

Clinical characteristics and endoscopic findings of the study subjects

In this study, 100 patients were diagnosed with EoE. Of these, 95 with EoE were matched with controls. We excluded five patients, because one subject was aged < 18 years; one did not undergo matching with controls and three current intake of PPIs. In contrast, 11,744 subjects underwent EGD during medical health check-up and 166 subjects with gastrointestinal cancer, history of gastrointestinal surgery, and EoE were excluded. We also excluded eight patients because of poor study results with food residue. Subsequently, 190 age- and sex-matched controls were randomly selected. These 190 controls did not have intake of PPIs.

The clinical characteristics and endoscopic findings of the subjects with EoE are summarized in Table 1. There were no significant differences between the two groups in terms of BMI, current alcohol consumption status, and current smoking status. The agreement of endoscopic findings of BE between two estimators was substantial (kappa coefficient = 0.639). The prevalence rate of BE was significantly lower in patients with EoE than in controls (2.1% vs. 13.2%; $p = 0.00528$). In detail, the prevalence rate of short-segment BE (SSBE) was significantly lower in patients with EoE than in controls (absence, 10 mm ≦, 20 mm ≦, and 30 mm ≦; 97.9%, 2.1%, 0%, and 0% vs. 86.8%, 10.6%, 2.6%, and 0%, respectively; $p = 0.00849$). Long-segment BE (LSBE) was not observed in both groups. In contrast, the prevalence of RE was higher in EoE patients than in controls, but it was not statistically significant (absence and Grades A, B, and C; 74.7%, 18.9%, 5.3%, and 1.1% vs. 83.7%, 12.6%, 3.7%, and 0%, respectively; $p = 0.193$). The prevalence of hiatal hernia was not significantly different between EoE patients and controls (22.1% vs. 17.9%; $p = 0.490$). The prevalence of atrophic gastritis was also not significantly different between EoE patients and controls (18.9% vs. 20.5%; $p = 0.875$).

Multivariate analysis to evaluate the association of BE with EoE

The results of multivariate analysis are shown in Table 2. Multivariate analysis showed that BE was significantly negatively associated with EoE (OR 0.132; 95% CI 0.0302–0.573; $p = 0.00686$). In contrast, BMI was positively associated with EoE (OR 1.80; 95% CI 1.050–3.10; $p = 0.0336$).

Discussion

Our study showed that BE was significantly negative associated with EoE. To the best of our knowledge, this is the first report to show these results in a comparison between EoE patients and controls. This result was consistent with the previous reports. There are only a few case reports of patients with both BE and EoE [16, 17]. Saboorian et al. reported that there was an inverse association between BE and EoE, which was investigated using a national pathological database in the United States [18].

EoE, BE, and GERD share common risk factors. Our study showed a positive association between EoE and BMI. This result seemed to be reflected that BMI was a risk factor for GERD. The systematic review and meta-analysis of EoE reported that about 20% of EoE patients had RE in the lower esophagus [19]. Although we compared the prevalence of BE in both EoE patients and matched controls, the previous reports showed that BE was also strongly associated with RE. Manabe et al. reported that, in patients with short-segment BE, the predictors of its elongation were the presence of RE in Japan [20]. However, our study showed that BE had a significantly negative association with EoE, although there were common mechanisms between EoE and BE from a viewpoint of GERD and Th2 cytokines.

The mechanism behind the inverse relation between BE and EoE is unclear. We speculate that one condition prevents the other. In terms of reflex content, bile acid promotes the

Table 1 Clinical characteristics and endoscopic finding of the study subjects and crude OR for EoE

Variable	Controls [$n=190$]	EoE [$n=95$]	Crude OR [95% CI]	p
Age, years [mean ± SD]	45.9 ± 10.5	45.9 ± 10.5		1.00
Sex				1.00
Female	76 [40.0%]	38 [40.0%]	1.00 [Reference]	
Male	114 [60.0%]	57 [60.0%]	1.00 [0.588–1.71]	
BMI, kg/m^2				0.0732
< 25	141 [74.2%]	60 [63.2%]	1.00 [Reference]	
≥ 25	49 [25.8%]	35 [36.8%]	1.675 [0.952–2.94]	
Current smoking				0.0802
Absent	153 [80.5%]	85 [89.5%]	1.00 [Reference]	
Present	37 [19.5%]	10 [10.5%]	0.488 [0.206–1.06]	
Current alcohol drinking				0.165
Absent	123 [64.7%]	70 [73.7%]	1.00 [Reference]	
Present	67 [35.3%]	25 [26.3%]	0.657 [0.363–1.16]	
Barrett's esophagus				0.00528*
Absent	165 [86.8%]	93 [97.9%]	1.00 [Reference]	
Present	25 [13.2%]	2 [2.1%]	0.131 [0.0150–0.541]	
Reflux esophagitis				0.193
Absent	159 [83.7%]	71 [74.7%]	1.00 [Reference]	
Grade A	24 [12.6%]	18 [18.9%]	1.68 [0.803–3.45]	
Grade B	7 [3.7%]	5 [5.3%]	1.60 [0.386–6.07]	
Grade C	0 [0%]	1 [1.1%]	NA	
Hiatal hernia				0.490
Absent	156 [82.1%]	74 [77.9%]	1.00 [Reference]	
Present	34 [17.9%]	21 [22.1%]	1.30 [0.668–2.49]	
Atrophic gastritis				0.875
Absent	151 [79.5%]	77 [81.1%]	1.00 [Reference]	
Present	39 [20.5%]	18 [18.9%]	0.905 [0.456–1.747]	

Data are expressed as mean ± SD or numbers (percentage)

BMI body mass index, *CI* confidence interval, *EoE* eosinophilic esophagitis, *OR* odds ratio, *SD* standard deviation

*$p < 0.05$

Table 2 Multivariate analysis to evaluate the association of various factors with EoE

Variables	OR	95% CI	p
Barrett's esophagus	0.132	0.0302–0.573	0.00686*
Reflux esophagitis	1.55	0.972–2.48	0.0654
Current alcohol drinking	0.678	0.381–1.21	0.185
Current smoking	0.493	0.230–1.060	0.0695
BMI	1.80	1.050–3.10	0.0336*

BMI body mass index, *CI* confidence interval, *EoE* eosinophilic esophagitis, *OR* odds ratio

*$p < 0.05$

development of BE [21]. It is possible that bile acid controls eosinophilic infiltrates in the esophageal mucosa. For the genetic factors responsible for EoE and BE, a genome-wide association study reported that the expression of EoE is related to TSLP, CAPN-14, and eotaxin 3 [7, 22]. In contrast, the development of BE is associated with four loci within or near MHC, FOXF1, GDF7, and TBX5 [23]. These genetic factors may control the association between BE and EoE. It is also possible that esophageal microbiome and food antigens influence the negative association between BE and EoE. Moreover, the difference in the immune response led to the association of BE and EoE. Genetic susceptibility and epigenetic factors may influence the differences in Th2 immune responses. Moreover, there is a possibility that eosinophilic infiltration may prevent the development of BE. We speculate that this study may imply that there is a different pathophysiology between BE and EoE in terms of many factors including reflux contents, gastric factors, microbiome, food antigens, and Th2 immune responses. The scheme of our hypothesis is shown in Fig. 2. However, the precise mechanism(s) remain unclear and further studies are needed in the future.

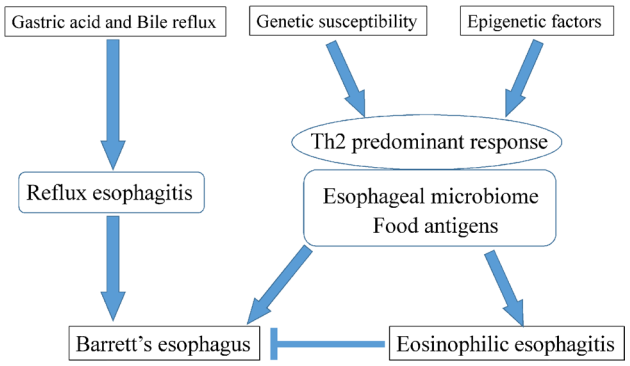

Fig. 2 Scheme of mechanism(s) underlying the association among Barrett's esophagus (BE), eosinophilic esophagitis (EoE), and reflux esophagitis (RE). We speculate that this study may imply that there is a different pathophysiology between BE and EoE in terms of many factors including reflux contents, microbiome, food antigens, and T helper (Th) 2-mediated immune responses. The possibility that EoE prevents the development of BE may deserve to be explored

The present study had some limitations. First, we made the diagnosis of BE endoscopically without obtaining histological confirmation of intestinal metaplasia. The American College of Gastroenterology defines BE as endoscopically recognizable columnar metaplasia of the esophageal mucosa that is confirmed to show intestinal metaplasia on the examination of mucosal biopsy specimens [24], which is the most widely accepted definition. However, in Japan, BE was diagnosed for the columnar epithelium continuous from the stomach with or without intestinal metaplasia [11]. The second limitation is concerning the accuracy of the endoscopic measurements of BE length. The previous studies have revealed that endoscopic measurement of the axial length of esophageal columnar epithelium is not necessarily reliable [25]. In this study, the prevalence rate of BE ≥ 1 cm in controls was 13.2%. The previous cross-sectional study in a Japanese population showed that the prevalence of BE ≥ 1 cm was 5.6% [26]. The prevalence of BE in this study was higher as compared to the previous reports, which might be associated with the judgement of the length. We measured BE length using forceps to obtain objective data and our results might be reliable, because the agreement of two estimators was substantial by kappa analysis. Third, the external validity of this report was low because of its retrospective and single-center nature. Further research with a multicenter study may overcome this limitation. Fourth, we did not perform esophageal biopsy in the control group. Therefore, we could not rule out the possibility of subjects with esophageal eosinophilia rarely being included as controls. However, it was valid to consider these subjects as controls, because they had no symptoms associated with esophageal motor dysfunction caused by eosinophilia.

In conclusion, BE is negatively associated with EoE in Japanese subjects. The mechanism of this inverse relationship should be examined in future.

Acknowledgements ST, FT, and YF were involved in study conception and design. ST and FT had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of data analysis. KO and SF acquired the data. ST and FT analyzed and interpreted the data. Drafting of the manuscript was performed by ST and FT. Critical revision of the manuscript for important intellectual content was conducted by ST, FT, KO, SH, YN, NK, KT, HY, TT, SF, TW, and YF. All authors have approved the final draft of this manuscript.

Compliance with ethical standards

Ethical Statement This study was conducted in accordance with the Declaration of Helsinki and its amendments. The study protocol was approved by the Ethics Committee of the Osaka City University Graduate School of Medicine (No. 3951).

Conflict of interest The authors declare no conflict of interests for this article.

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