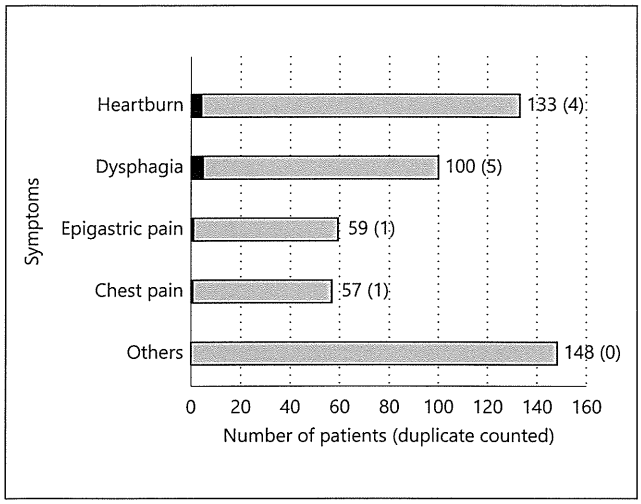

Fig. 3. Summary of symptoms. Symptoms noted in the enrolled patients (symptomatic group; n = 319) are shown as a bar chart (497 symptoms, duplicates counted). Others included acid regurgitation, nausea, and vomiting. Patients with EE are shown as a closed bar in each column.

Table 2. Baseline characteristics between EE-positive and EE-negative subjects

	EE positive	EE negative
Total subjects	12	337
Men:women	7:5	156:181
Age, years		
Mean ± SD	49.3±21.8	62.9±14.9
Range	24–82	22–88
Concurrent allergic disease (duplicates counted)		
Asthma	2	6
Atopic dermatitis	1	8
Hay fever	1	11
Food allergy	1	5
Others	1	11

Table 3. Diagnostic utility for EE by presenting symptoms

Symptoms	b	Exp (b)	Exp (b) 95% CI	p value
Dysphagia	0.384	1.469	8.796–983.727	0.566
Heartburn	−0.317	0.729	0.192–13.509	0.657
Epigastric pain	−0.498	0.608	0.875–289.243	0.641
Chest pain	−17.814	0.000	0.851–28.0	0.997

b = Partial regression coefficient; Exp (b) = odds ratio; CI = confidence interval.

in patients with EE, though the difference was not significant (62.5 vs. 30.4%, p = 0.054). Indeed, the patients with EE accounted for only 5% (5/100) of all patients who complained of dysphagia. Although present in some of the EE patients, the ratios of those with heartburn, epigastric pain, and chest pain were also not significantly different from those among non-EE patients (n = 311). Next, we examined 4 major symptoms (heartburn, dysphagia, epigastric pain, chest pain) for usefulness in diagnosis of EE. The partial regression coefficient value for all of the items was <1, indicating that none of the presenting symptoms was useful for EE diagnosis (table 3).

Endoscopic Findings More Important Than Symptoms to Predict EE

Of the patients with symptoms suggesting EoE (group 1), 30 had abnormal endoscopic findings suspicious of EoE (group 1a), while 289 had no such endoscopic findings (group 1b). Interestingly, 7 patients in group 1a (23.3%; 7/30) were diagnosed with EE, while 1 patient was diagnosed as EE in group 1b (0.35%; 1/289). Therefore, the presence of abnormal endoscopic findings was significantly more important to predict EE in symptomatic patients. In other words, the frequency of EE was quite low in patients with symptoms but no endoscopic findings. Moreover, 4 patients among asymptomatic patients with abnormal endoscopic findings (group 2; 13.3%; 4/30) were diagnosed with EE, suggesting the importance of endoscopic findings to predict EE.

Presence of Linear Furrows Was the Most Reliable for Diagnosis of EE

Among all 349 patients examined, 60 had typical endoscopic findings of EoE including linear furrows (n = 30), whitish exudates (n = 23), multiple concentric rings (n = 13), and reddening (n = 8), with some overlap (fig. 4). Patients with endoscopic findings suspicious of EoE consisted of both symptomatic (n = 30, group 1a) and asymptomatic (n = 30, group 2) patients. Eleven (18.3%) of 60 patients with endoscopic findings were diagnosed as EE, and linear furrows were seen in 10 (90.9%), while other findings were not so frequent (table 1). Overall, 33.3% (10/30) of the patients with linear furrows were histologically diagnosed with EE.

Next, we examined 5 major endoscopic findings (linear furrows, multiple concentric rings, whitish exudates, reddening, others) to examine their diagnostic utility for EE. Linear furrows were the most reliable, as

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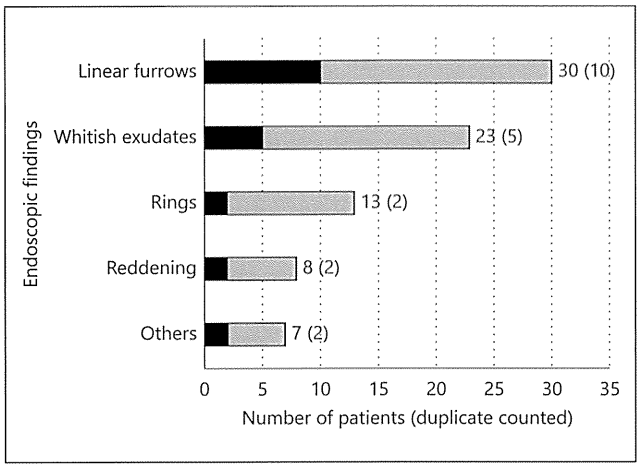

Fig. 4. Summary of endoscopic findings. Endoscopic findings suspicious of EoE in enrolled patients are shown as a bar chart. Others included edema, pallor, and decreased vascularity. Patients with EE are shown as a closed bar in each column.

Table 4. Diagnostic utility for EE by endoscopic findings

Endoscopic findings	b	Exp (b)	Exp (b) 95% CI	p value
Linear furrows	3.728	41.583	2.936–588.879	0.006
Rings	0.076	1.079	0.139–8.360	0.942
Whitish exudates	1.355	3.876	0.704–21.348	0.120
Reddening	1.751	5.763	0.375–88.660	0.209
Others	0.890	2.435	0.224–26.523	0.465

shown by partial regression coefficient analysis (table 4), with an odds ratio of 41.583, which was the only statistically significant finding ($p = 0.006$). The probability of correctly diagnosing EE based on the presence of linear furrows was 87.3%. However, the sensitivity for linear furrows was modest at 83%, whereas specificity was 95%. Furthermore, the positive predictive value was 37% and the negative predictive value was 99% (table 5).

Discussion

This is the first reported investigation comparing the diagnostic utility of symptoms and endoscopic findings for EE in a Japanese population. We conducted the present multicenter prospective study of 349 patients taken from biopsy samples because of suspicious symptoms and/or endoscopic abnormalities. Symptoms suggesting esophageal dysfunction were noted in 319 cases and abnormal endoscopic findings were found in 60. Our findings showed that the prevalence of EE was 2.5% (8/319), and 5% (5/100) for patients with esophageal symptoms, and dysphagia, respectively. Of 8 patients with EE, 3 were finally diagnosed with EoE after PPI trial. The recent study conducted in USA by Dellon et al. [28] has shown that EE was found in 38% (66/173) of patients with dysphagia. In that study, 40 of 66 patients with EE were confirmed to have EoE and 24 had PPI-REE after PPI trial. Consistent with recent findings [29], no clinical or endoscopic feature independently distinguished PPI-REE from EoE before the PPI trial. In addition, there were no differences between the 2 patient groups for histological findings including amount of eosinophil infiltration and degree of inflammatory cell infiltration in this study. The prevalence of EE may be affected by the proportion of GERD patients in enrolled patients. Although patients with endoscopically proven reflux esophagitis were excluded, most of symptomatic GERD patients could be enrolled in this study. Indeed, 38.1% (133/349) of the patients had heartburn and 39.0% continued to take PPI when EGD was scheduled, while only patients with dysphagia were enrolled in the study by Dellon et al. [28]. Nonetheless, our data indicate that both EE and EoE are uncommon among patients with chest or epigastric symptoms in a Japanese population as compared with Western populations.

As for clinical features, the most common symptom among Japanese patients with EoE is dysphagia, and none of the patients in our previous study had a history of food impaction [7], a common symptom associated with EoE in Western individuals [18], especially Caucasians, suggesting racial differences with regard to EoE-related symptoms. Dysphagia is consistently the most common symptom reported by patients with EE. Although the ratio of dysphagia was higher in our patients with EE (62.5%) than in those without EE (30.4%), subjective symptoms including dysphagia, heartburn, and chest pain were not specific enough to make a diagnosis of EE, which was shown by logistic regression analysis.

A strength of this study is that an esophageal biopsy was performed in all of the enrolled patients with symptoms suggesting esophageal dysfunction with or without endoscopic abnormalities (n = 319). Interestingly, only a single patient (0.35%) was diagnosed with EE among those with normal endoscopy findings, as compared with 18.3% (11/60) of the patients with abnormal findings.

Table 5. Sensitivity, specificity, and predictive value of endoscopic findings

	Linear furrows	Rings	Whitish exudates	Reddening
Sensitivity	83 (75–91)	17 (4–38)	42 (14–70)	17 (4–38)
Specificity	95 (93–97)	97 (95–99)	95 (93–97)	98 (97–99)
PPV	37 (28–46)	15 (11–19)	22 (6–38)	25 (–5 to 55)
NPV	99 (98–100)	98 (96–100)	98 (96–100)	97 (95–99)

Figures indicate percentages (95% CI). PPV = Positive predictive value; NPV = negative predictive value.

Consistent with our results, Mackenzie et al. [30] prospectively assessed the risk factors and prevalence of EoE in an adult population with dysphagia. Of 261 patients with dysphagia, 31 (12%) met the pathological criteria for EE, while EE was found only in 5 cases (1.9%) without suspicious endoscopic findings. These findings contradict the routine esophageal biopsies for the purpose of detecting EE in patients without abnormal endoscopic findings suggesting EoE. An esophageal biopsy procedure may not be useful or cost-effective to determine EoE in symptomatic patients without abnormal endoscopic findings. However, in patients with abnormal endoscopic findings suspicious of EoE, irrespective of symptoms, biopsy samples should be taken from the esophagus to determine the presence of EE.

Endoscopic abnormalities in patients with EoE can vary within a wide range, including esophageal rings, linear furrows, strictures, and whitish exudates [24, 31]. There may also be racial differences in EoE-related endoscopic findings [19, 20]. In the present study, only 2 (16.7%) of the patients with EE had esophageal rings and none had esophageal strictures. Consistently, we previously confirmed that rings and strictures were not frequent in patients with EE or EoE in a Japanese population, in contrast to Western populations [25]. In addition, the present study revealed that linear furrows were the most frequent endoscopic findings in patients with EE as they were found in 83.3% (10/12), while only 1 (8.3%) of the patients with EE had no characteristic endoscopic finding. In our previous report, approximately 40% of patients with EoE had no specific endoscopic findings [7]. These differences may be related to not only study design but also awareness of the disease among Japanese endoscopists, as it has been widely reported. According to a recent meta-analysis, prospective studies showed that at least 1 abnormality was detected by endoscopy in 93% of EoE patients [25]. Therefore, endoscopic findings suspicious of EE, especially linear furrows, can be detected in most patients with EE by an experienced endoscopist with careful observation using a high-resolution or narrow-band imaging endoscopy [32].

Among the various endoscopic findings noted in the present study, linear furrows were the most useful for diagnosis of EE, as shown by logistic regression analysis. A previous pooled analysis of several studies showed modest sensitivity for EoE, such as 48% for linear furrows, 44% for corrugated rings, and 27% for whitish exudates [25], whereas sensitivities for EE in the present study were found to be 83, 17, and 42%, respectively. These suggest that the endoscopic finding of linear furrows is the most important for detection of EE in Japanese individuals. Recently, Hori et al. [33] investigated the diagnostic utility of endoscopic features for EE. Although the numbers of cases of EE (n = 5) were lower as compared to our study, the diagnostic utility of linear furrows and corrugated rings for EE was found to be superior to white exudates. Importantly, the results of interobserver agreement in a study of endoscopic findings of EoE indicated that gastroenterologists identified rings ($\kappa = 0.56$) and furrows ($\kappa = 0.48$) with fair to good reliability, whereas they did not reliably identify white exudate ($\kappa = 0.29$) by white-light endoscopy and narrow-band imaging endoscopy [34].

Here, we focused on patients with EE, which is essential for diagnosis of EoE. If dense eosinophilic infiltration is found in esophageal epithelium, EoE, GERD, and PPI-REE are the most common clinical possibilities. Recent clinical guidelines strongly recommend a PPI trial for such patients, and patients with persistent eosinophilic infiltration and symptoms after such a trial can be formally diagnosed with EoE [9, 10]. However, the appropriateness of this strategy for diagnosis of EoE remains to be elucidated. Gastric acid might play a role in the pathogenesis of EoE, and PPIs are effective in some cases via decreasing esophageal acid exposure [12, 35, 36]. Moreover,

a number of potential anti-inflammatory effects of PPIs have been described [37], suggesting that those drugs have anti-inflammatory actions independent of their effects on gastric acid secretion [15, 16]. Thus, EoE patients might benefit from PPI therapy regardless of whether they have coexisting GERD. Additional studies are sorely needed to recognize, define, and mechanistically understand PPI-REE [11, 38]. Nonetheless, long-term clinical outcome in patients with EE should be clarified in the future study.

In summary, EE remains a rare condition among Japanese patients with chest and epigastric symptoms. Reported symptoms including dysphagia do not lend support to a diagnosis of EE in Japanese cases. As for endoscopic findings, the presence of linear furrows was the most frequent and useful for EE diagnosis.

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Disclosure Statement

The authors have no conflict of interest to declare.

References

1 Dellon ES: Diagnosis and management of eosinophilic esophagitis. Clin Gastroenterol Hepatol 2012;10:1066–1078.
2 Furuta GT, Liacouras CA, Collins MH, Gupta SK, Justinich C, Putnam PE, Bonis P, Hassall E, Straumann A, Rothenberg ME: Eosinophilic esophagitis in children and adults: a systematic review and consensus recommendations for diagnosis and treatment. Gastroenterology 2007;133:1342–1363.
3 Prasad GA, Alexander JA, Schleck CD, Zinsmeister AR, Smyrk TC, Elias RM, Locke GR 3rd, Talley NJ: Epidemiology of eosinophilic esophagitis over three decades in Olmsted county, Minnesota. Clin Gastroenterol Hepatol 2009;7:1055–1061.
4 Sealock RJ, Rendon G, El-Serag HB: Systematic review: the epidemiology of eosinophilic oesophagitis in adults. Aliment Pharmacol Ther 2010;32:712–719.
5 Fujishiro H, Amano Y, Kushiyama Y, Ishihara S, Kinoshita Y: Eosinophilic esophagitis investigated by upper gastrointestinal endoscopy in Japanese patients. J Gastroenterol 2011; 46:1142–1144.
6 Joo MK, Park JJ, Kim SH, Kim KH, Jung W, Yun JW, Lee BJ, Kim JH, Yeon JE, Kim JS, Byun KS, Lee SW, Bak YT: Prevalence and endoscopic features of eosinophilic esophagitis in patients with esophageal or upper gastrointestinal symptoms. J Dig Dis 2012;13:296–303.
7 Kinoshita Y, Furuta K, Ishimura N, Ishihara S, Sato S, Maruyama R, Ohara S, Matsumoto T, Sakamoto C, Matsui T, Ishikawa S, Chiba T: Clinical characteristics of Japanese patients with eosinophilic esophagitis and eosinophilic gastroenteritis. J Gastroenterol 2013;48: 333–339.
8 Shi YN, Sun SJ, Xiong LS, Cao QH, Cui Y, Chen MH: Prevalence, clinical manifestations and endoscopic features of eosinophilic esophagitis: a pathological review in China. J Dig Dis 2012;13:304–309.
9 Dellon ES, Gonsalves N, Hirano I, Furuta GT, Liacouras CA, Katzka DA; American College of Gastroenterology: ACG clinical guideline: evidenced based approach to the diagnosis and management of esophageal eosinophilia and eosinophilic esophagitis (EoE). Am J Gastroenterol 2013;108:679–692.
10 Liacouras CA, Furuta GT, Hirano I, Atkins D, Attwood SE, Bonis PA, Burks AW, Chehade M, Collins MH, Dellon ES, Dohil R, Falk GW, Gonsalves N, Gupta SK, Katzka DA, Lucendo AJ, Markowitz JE, Noel RJ, Odze RD, Putnam PE, Richter JE, Romero Y, Ruchelli E, Sampson HA, Schoepfer A, Shaheen NJ, Sicherer SH, Spechler S, Spergel JM, Straumann A, Wershil BK, Rothenberg ME, Aceves SS: Eosinophilic esophagitis: updated consensus recommendations for children and adults. J Allergy Clin Immunol 2011;128:3–20.
11 Cheng E: Proton pump inhibitors for eosinophilic oesophagitis. Curr Opin Gastroenterol 2013;29:416–420.
12 Molina-Infante J, Katzka DA, Gisbert JP: Review article: proton pump inhibitor therapy for suspected eosinophilic oesophagitis. Aliment Pharmacol Ther 2013;37:1157–1164.
13 Molina-Infante J, Zamorano J: Distinguishing eosinophilic esophagitis from gastroesophageal reflux disease upon PPI refractoriness: what about PPI-responsive esophageal eosinophilia? Digestion 2012;85:210.
14 von Arnim U, Wex T, Rohl FW, Neumann H, Kuster D, Weigt J, Monkemuller K, Malfertheiner P: Identification of clinical and laboratory markers for predicting eosinophilic esophagitis in adults. Digestion 2011;84:323–327.
15 Cheng E, Zhang X, Huo X, Yu C, Zhang Q, Wang DH, Spechler SJ, Souza RF: Omeprazole blocks eotaxin-3 expression by oesophageal squamous cells from patients with eosinophilic oesophagitis and GORD. Gut 2013;62: 824–832.
16 Zhang X, Cheng E, Huo X, Yu C, Zhang Q, Pham TH, Wang DH, Spechler SJ, Souza RF: Omeprazole blocks STAT6 binding to the eotaxin-3 promoter in eosinophilic esophagitis cells. PLoS One 2012;7:e50037.
17 Spergel JM, Brown-Whitehorn TF, Beausoleil JL, Franciosi J, Shuker M, Verma R, Liacouras CA: 14 years of eosinophilic esophagitis: clinical features and prognosis. J Pediatr Gastroenterol Nutr 2009;48:30–36.
18 Straumann A, Spichtin HP, Grize L, Bucher KA, Beglinger C, Simon HU: Natural history of primary eosinophilic esophagitis: a follow-up of 30 adult patients for up to 11.5 years. Gastroenterology 2003;125:1660–1669.
19 Bohm M, Malik Z, Sebastiano C, Thomas R, Gaughan J, Kelsen S, Richter JE: Mucosal eosinophilia: prevalence and racial/ethnic differences in symptoms and endoscopic findings in adults over 10 years in an urban hospital. J Clin Gastroenterol 2012;46:567–574.
20 Sperry SL, Woosley JT, Shaheen NJ, Dellon ES: Influence of race and gender on the presentation of eosinophilic esophagitis. Am J Gastroenterol 2012;107:215–221.
21 Dellon ES, Gibbs WB, Fritchie KJ, Rubinas TC, Wilson LA, Woosley JT, Shaheen NJ: Clinical, endoscopic, and histologic findings distinguish eosinophilic esophagitis from gastroesophageal reflux disease. Clin Gastroenterol Hepatol 2009;7:1305–1313.

22 Kinoshita Y, Furuta K, Ishimura N, Ishihara S: Elevated plasma cytokines in Japanese patients with eosinophilic esophagitis and gastroenteritis. Digestion 2012;86:238–243.
23 Lundell LR, Dent J, Bennett JR, Blum AL, Armstrong D, Galmiche JP, Johnson F, Hongo M, Richter JE, Spechler SJ, Tytgat GN, Wallin L: Endoscopic assessment of oesophagitis: clinical and functional correlates and further validation of the Los Angeles classification. Gut 1999;45:172–180.
24 Hirano I, Moy N, Heckman MG, Thomas CS, Gonsalves N, Achem SR: Endoscopic assessment of the oesophageal features of eosinophilic oesophagitis: validation of a novel classification and grading system. Gut 2013;62:489–495.
25 Kim HP, Vance RB, Shaheen NJ, Dellon ES: The prevalence and diagnostic utility of endoscopic features of eosinophilic esophagitis: a meta-analysis. Clin Gastroenterol Hepatol 2012;10:988–996.
26 Yerian L, Fiocca R, Mastracci L, Riddell R, Vieth M, Sharma P, Franzen S, Fernstrom P, Ruth M: Refinement and reproducibility of histologic criteria for the assessment of microscopic lesions in patients with gastroesophageal reflux disease: the Esohisto Project. Dig Dis Sci 2011;56:2656–2665.
27 Fiocca R, Mastracci L, Riddell R, Takubo K, Vieth M, Yerian L, Sharma P, Fernstrom P, Ruth M: Development of consensus guidelines for the histologic recognition of microscopic esophagitis in patients with gastroesophageal reflux disease: the Esohisto Project. Hum Pathol 2010;41:223–231.
28 Dellon ES, Speck O, Woodward K, Gebhart JH, Madanick RD, Levinson S, Fritchie KJ, Woosley JT, Shaheen NJ: Clinical and endoscopic characteristics do not reliably differentiate PPI-responsive esophageal eosinophilia and eosinophilic esophagitis in patients undergoing upper endoscopy: a prospective cohort study. Am J Gastroenterol 2013;108:1854–1860.
29 Moawad FJ, Schoepfer AM, Safroneeva E, Ally MR, Chen YJ, Maydonovitch CL, Wong RK: Eosinophilic oesophagitis and proton pump inhibitor-responsive oesophageal eosinophilia have similar clinical, endoscopic and histological findings. Aliment Pharmacol Ther 2014;39:603–608.
30 Mackenzie SH, Go M, Chadwick B, Thomas K, Fang J, Kuwada S, Lamphier S, Hilden K, Peterson K: Eosinophilic oesophagitis in patients presenting with dysphagia-a prospective analysis. Aliment Pharmacol Ther 2008;28:1140–1146.
31 Muller S, Puhl S, Vieth M, Stolte M: Analysis of symptoms and endoscopic findings in 117 patients with histological diagnoses of eosinophilic esophagitis. Endoscopy 2007;39:339–344.
32 Tanaka K, Rubio CA, Dlugosz A, Truskaite K, Befrits R, Lindberg G, Schmidt PT: Narrow-band imaging magnifying endoscopy in adult patients with eosinophilic esophagitis/esophageal eosinophilia and lymphocytic esophagitis. Gastrointest Endosc 2013;78:659–664.
33 Hori K, Watari J, Fukui H, Tanaka J, Tomita T, Sakurai J, Kondo T, Oshima T, Toyoshima F, Yamasaki T, Okugawa T, Miwa H: Do endoscopic features suggesting eosinophilic esophagitis represent histological eosinophilia? Dig Endosc 2014;26:156–163.
34 Peery AF, Cao H, Dominik R, Shaheen NJ, Dellon ES: Variable reliability of endoscopic findings with white-light and narrow-band imaging for patients with suspected eosinophilic esophagitis. Clin Gastroenterol Hepatol 2011;9:475–480.
35 Blanchard C, Stucke EM, Burwinkel K, Caldwell JM, Collins MH, Ahrens A, Buckmeier BK, Jameson SC, Greenberg A, Kaul A, Franciosi JP, Kushner JP, Martin LJ, Putnam PE, Abonia JP, Wells SI, Rothenberg ME: Coordinate interaction between IL-13 and epithelial differentiation cluster genes in eosinophilic esophagitis. J Immunol 2010;184:4033–4041.
36 Molina-Infante J, Ferrando-Lamana L, Ripoll C, Hernandez-Alonso M, Mateos JM, Fernandez-Bermejo M, Duenas C, Fernandez-Gonzalez N, Quintana EM, Gonzalez-Nunez MA: Esophageal eosinophilic infiltration responds to proton pump inhibition in most adults. Clin Gastroenterol Hepatol 2011;9:110–117.
37 Kedika RR, Souza RF, Spechler SJ: Potential anti-inflammatory effects of proton pump inhibitors: a review and discussion of the clinical implications. Dig Dis Sci 2009;54:2312–2317.
38 Hirano I: Should patients with suspected eosinophilic esophagitis undergo a therapeutic trial of proton pump inhibition? Am J Gastroenterol 2013;108:373–375.

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Dear Editor

Eosinophilic Gastroenteritis Treated with a Multiple-Food Elimination Diet

Primary eosinophilic gastrointestinal disorders (EGIDs) include eosinophilic esophagitis (EoE), gastroenteritis (EGE), and colitis.[1,2] Recently, an empiric diet, preferentially devoid of the 6 most common food-allergens, milk, soy, egg, wheat, peanuts/tree nuts, and shellfish/fish (6-FED) has been used for EoE.[3,4] The 6-FED induced a significant improvement, which was equivalent to that of topical steroids in EoE.[5] In contrast to EoE, 6-FED has never been employed for the treatment of EGE as far as we know.

Here, we report a case of a patient with EGE successfully treated with the elimination of these 6 foods and other the patient's historically causative foods (multiple foods elimination diet; MFED).

CASE REPORT

A 5-year and 11-month-old boy was referred to our institution because of urticaria, abdominal pain, diarrhea, and bloody stool starting 3 months prior. He frequently experienced abdominal pain and vomiting after eating various foods, especially chicken, pork, and beef. He was treated with oral steroids and antihistamines for urticaria in another institution. However, only temporary remission in digestive symptoms as well as urticaria was observed. He had been treated for asthma as an outpatient. He had a history of colon-polyps and bloody stool associated with lymphoid hyperplasia at 2 and 3 years of age, respectively. After visiting our institution, he underwent upper gastrointestinal endoscopic examination, which revealed circumferential redness, edema, and erosion of the duodenum (Fig. 1A-a). The biopsy showed hyperemia and bleeding with eosinophil and lymphocyte infiltration in the duodenal lamina propria (Fig. 1 A-b). Eight days after upper gastrointestinal endoscopy, the patient was admitted to another institution because of sudden abdominal pain and diarrhea soon after eating Sichuan-style bean-curd containing soybean, chicken, and pork and then referred to our hospital owing to the computed tomography findings: extensive bowel wall edema. Rectal wall thickening was also evidenced by ultrasound (Fig. 1B-a). Sigmoidal biopsies revealed hypereosinophilia (36 eosinophils/high-power-field, Fig. 1A-c). Therefore, the patient was diagnosed with EGE.[6,7] There was a wide variety of possible causative foods, which made it difficult to pinpoint each food. The antigen-specific IgE antibody

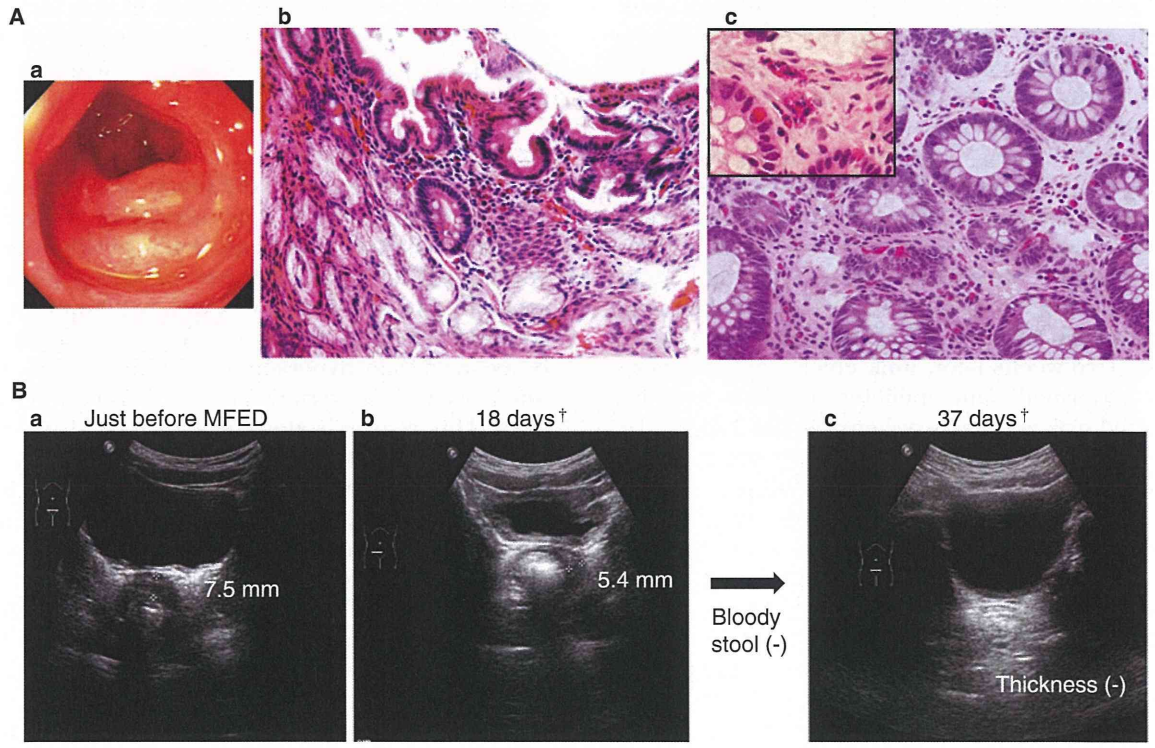

Fig. 1 Endoscopic findings of duodenum (**A-a**). Histological findings of duodenum (**A-b**) and sigmoidal colon (**A-c**) in hematoxylin and eosin-stained sections (Optical magnifications: **A-b** and **c**, ×200, inset in **c** ×400). Ultrasound findings of rectum (**B-a-c**, †days after first ultrasound). MFED, multiple foods elimination diet.

Table 1 Total and antigen-specific IgEs before MFED

Total IgE (IU/ml)	1145
Antigen-specific IgEs (U_A/mL)	
Milk	<0.35
Egg white	0.80
Wheat	0.51
Soybean	0.40
Peanuts	0.54
Sesame	1.03
Crab	<0.35
Shrimp	<0.35
Mackerel	<0.35
Scallop	<0.35
Pork	<0.35
Chicken	<0.35
Beef	<0.35
House dust	>100
Mite	>100
Cedar pollen	17.7

test results are shown in Table 1. In addition, oral steroids yielded poor results as mentioned above. Therefore, he was recommended a MFED, which involved the 6-FED as listed above and meats when combined with an elemental diet (ED). Antihistamines and suplatast tosilate were also administered. One month later, the bloody stool and urticaria resolved, although transient exacerbation of urticaria due to respiratory infection occurred, and the rectal wall thickening was improved (Fig. 1B-b, c). One month later, the patient presented vomiting due to accidental consumption of sweets, including chocolate and wheat. To minimize the eliminated foods and shorten the elimination period, challenge tests were scheduled immediately. About 2.5 months after treatment initiation, a soybean challenge test was blindly performed using 1 g of bean curd. The patient developed erythema, facial swelling, and urticaria within 30 minutes. Two weeks later, milk challenge tests were blindly performed. One milliliter of cow's milk induced mild urticaria and erythema within 1 hour. To confirm these results, 5 ml of cow's milk was administered the next day. The patient developed emesis within 30 minutes of milk consumption followed by generalized erythema and urticaria. Diarrhea and bloody stool persisted for a few weeks. Approximately 5 months after the beginning of MFED, serial reintroduction was initiated after the discontinuation of anti-histamines and suplatast tosilate, as the patient had been asymptomatic for almost 4 months except when consumed accidentally. The reintroduction phase consisted of the addition of 1-food group every 1-2 weeks (Fig. 2). Mild symptoms were presented but not exacerbated. Therefore, we were able to continue with the reintroduction phase, except when the patient presented with influenza. Foods were successfully reintroduced. Peanuts/tree nuts and shellfish were not challenged, as they were not necessary for his nutrition. Bloody stool recurred 1 month after the completed reintroduction. In addition, he had presented vomiting after eating dairy products, eggs, bean-curd, and sausages and more varied foods behind the back of his mother. Subsequently, a colonoscopy was performed, which indicated sigmoidal wall edema. The biopsy presented eosinophilic infiltration. MFED was initiated again. Symptoms disappeared in a few weeks and sigmoidal wall edema was improved. Therefore, the reintroduction phase was initiated once more. As the symptoms were milder than before, foods were reintroduced every 3 days. The reintroduction phase was completed without any major symptoms (shown in Fig. 2 until this point). About 4 months later, the patient presented with intermittent vomiting with mild abdominal pain, which were mostly self-limited and occasionally required antihistamines. Subsequently, symptoms were accompanied with urticaria. According to the medical history, the symptoms were exacerbated by cow milk, and thus dairy products were eliminated from his diet. Colonic mucosal edema and eosinophilic infiltration with lymphoid hyperplasia and Charcot-Leyden crystals were observed. Swollen mesenteric lymph nodes were identified by ultrasound. These symptoms resolved a month after elimination of dairy products. The improvement of swollen mesenteric lymph nodes was also confirmed. Subsequently, the patient achieved symptom remission while maintaining a dairy product-free diet.

DISCUSSION

EGIDs are recognized as a result of combined IgE and non-IgE mediated hypersensitivity. Consequently, the majority of patients have positive antigen-specific IgE antibody tests and/or skin-prick tests to multiple food-allergens but their symptoms lack the typical immediate response, which is considered to be delayed food hypersensitivity.[1] In fact, the symptoms occur at a variety of times, from minutes to days. This also indicates the difficulty of identifying the causative foods.[8] As a result, ED and systemic steroids have often been chosen for the treatment of EGE.[1,9] However, ED reduces quality of life[4] and systemic steroids are often accompanied by undeniable side effects. Therefore, we designed MFED for EGE based on those of EoE.[3,4] There is the possibility that the MFED against EGE allows the identification of possible causative foods during the reintroduction period as well as significant improvement of symptoms.[4] Indeed, the present case of EGE represents a significant improvement after MFED and the reintroduction process was helpful to identify the causative foods. Consequently, MFED could result in the unnecessary removal of foods and/or might not include

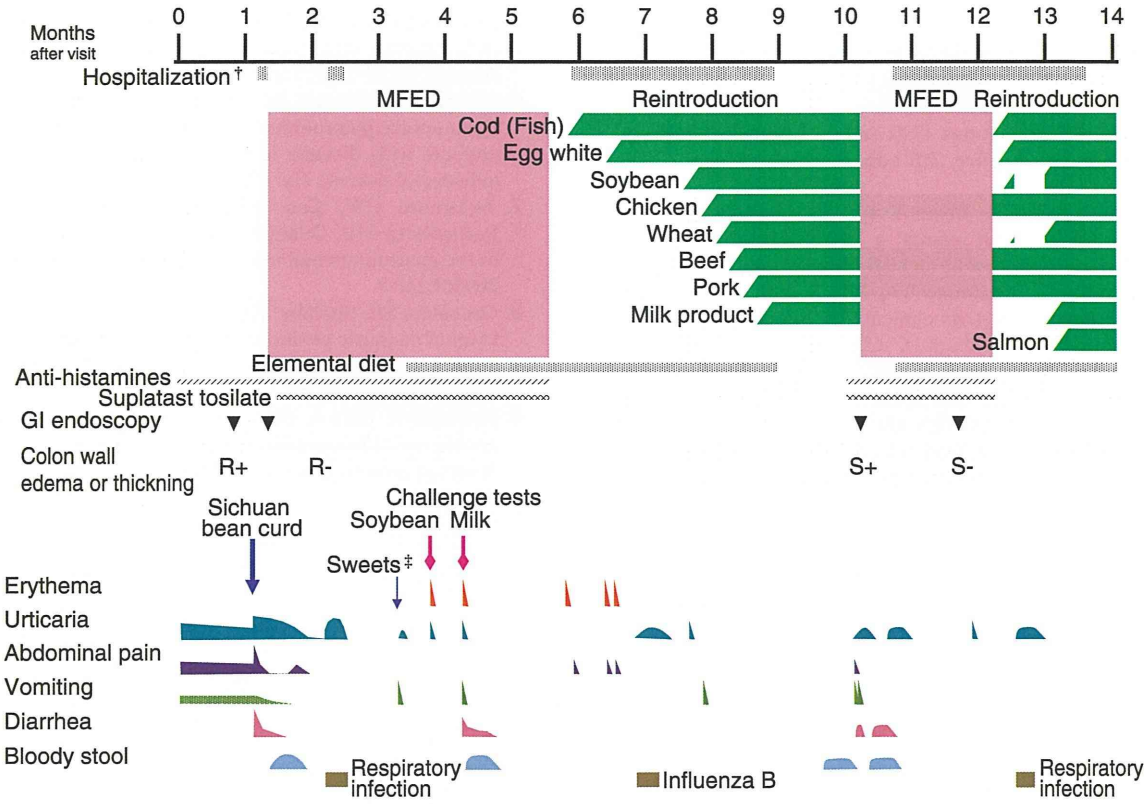

Fig. 2 Clinical course after visit of our institution containing 1st MFED, 1st serial reintroduction, 2nd MFED, and 2nd serial reintroduction. MFED, multiple foods elimination diet; GI, gastrointestinal; R, rectal wall thickning; S, sigmoidal colon edema. †Hospitalization due to treatments; ‡containing chocolate and wheat.

the true causative foods responsible for disease development. Therefore, ongoing efforts to identify the true causative foods and shorten the food elimination period are necessary. Herein, challenge tests for soybean and milk were performed in the first few months after initiating the MFED for earlier reintroduction. Challenge tests in preparation for reintroduction and accidental ingestion indicated that the patient was thought to be allergic at least to cow milk, soybean, and wheat in the early remission phase. In addition, cow milk was the most susceptible antigen for the patient as was indicated by the long-term follow-up. Nonetheless, elimination of his historically allergy-causative foods such as meats in addition to 6-FED could be effective, although the symptoms induced by these foods were not repeated, since they apparently induced symptoms in the early phase. Interestingly, long-term MFED induced successful reintroduction of the foods, suggesting that complete remission may take longer time. Moreover, when mildly relapsed, MFED with short-term reintroduction may be possible.

In conclusion, compared to ED, MFED can be easily applied and it demonstrates similar efficacy in identifying causative foods. Further, apparent side effects were not detected in the follow-up period. MFED is thought to be a promising alternative approach for EGE.

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Yoshiyuki Yamada[1], Masahiko Kato[1], Yuka Isoda[2], Akira Nishi[3], Yuko Jinbo[2] and Yasuhide Hayashi[4]

[1]Division of Allergy and Immunology, [2]Division of Nutrition and Cooking, [3]Division of Surgery and [4]Division of Hematology and Oncology, Gunma Children's Medical Center, Gunma, Japan

Email: yamaday@gcmc.pref.gunma.jp

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REFERENCES

1. Rothenberg ME. Eosinophilic gatroenteropathies. In: Adkinson NF Jr, Bochner BS, Busse WW, Holgate ST, Lemanske RF Jr, Simons FER (eds). *Middleton's Allergy: Principles and Practice,* 7th edn. St. Louis: Mosby, 2008; 879-91.
2. Yamada Y, Nishi A, Ebara Y *et al.* Eosinophilic gastrointestinal disorders in infants: a Japanese case series. *Int Arch Allergy Immunol* 2011;**155** (Suppl 1):40-5.
3. Kagalwalla AF, Sentongo TA, Ritz S *et al.* Effect of six-food elimination diet on clinical and histologic outcomes in eosinophilic esophagitis. *Clin Gastroenterol Hepatol* 2006;**4**:1097-102.
4. Gonsalves N, Yang GY, Doerfler B, Ritz S, Ditto AM, Hirano I. Elimination diet effectively treats eosinophilic esophagitis in adults; food reintroduction identifies causative factors. *Gastroenterology* 2012;**142**:1451-9. e1; quiz e14-5.
5. Liacouras CA. Clinical presentation and treatment of pediatric patients with eosinophilic esophagitis. *Gastroenterol Hepatol (N Y)* 2011;**7**:264-7.
6. Talley NJ, Shorter RG, Phillips SF, Zinsmeister AR. Eosinophilic gastroenteritis: a clinicopathological study of patients with disease of the mucosa, muscle layer, and subserosal tissues. *Gut* 1990;**31**:54-8.
7. DeBrosse CW, Case JW, Putnam PE, Collins MH, Rothenberg ME. Quantity and distribution of eosinophils in the gastrointestinal tract of children. *Pediatr Dev Pathol* 2006;**9**:210-8.
8. Orenstein SR, Shalaby TM, Di Lorenzo C *et al.* The spectrum of pediatric eosinophilic esophagitis beyond infancy: a clinical series of 30 children. *Am J Gastroenterol* 2000; **95**:1422-30.
9. Justinich C, Katz A, Gurbindo C *et al.* Elemental diet improves steroid-dependent eosinophilic gastroenteritis and reverses growth failure. *J Pediatr Gastroenterol Nutr* 1996; **23**:81-5.

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研究代表者　　野村　伊知郎

連絡先　〒157-8535　東京都世田谷区大蔵 2-10-1
国立成育医療研究センター
免疫アレルギー研究部
生体防御系内科部　アレルギー科
TEL：03-3416-0181　FAX：03-3416-2222