

Original Article



Clinical and endoscopic characteristics of eosinophilic esophagitis in Japan: a case-control study

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ABSTRACT

Background: Eosinophilic esophagitis (EoE) is an allergy-associated clinicopathologic condition gaining an increasing amount of recognition in various areas of the world. While the clinical definition and characteristics may differ depending on country and region, sufficient studies have not yet been performed in Japan.

Objective: To assess the prevalence of EoE among the Japanese population and the clinical features associated with the disease.

Methods: Endoscopic data from January 2012 to October 2018 was gathered from 9 Japanese clinical institutes. EoE, defined as esophageal mucosal eosinophilia of at least 15 eosinophils per high-power field, was determined based on esophageal biopsies. Clinical and endoscopic patterns in the cases with EoE were investigated and compared with 186 age- and sex-matched controls.

Results: From 130,013 upper endoscopic examinations, 66 cases of EoE were identified (0.051%; mean age, 45.2 years [range, 7–79 years]; 45 males). Twenty-five patients (37.9%) with EoE were diagnosed by endoscopy during a medical check-up. Patients with EoE had more symptoms (69.7% vs. 10.8%, $p < 0.01$) such as dysphagia and food impaction, and more allergies (65.2% vs. 23.7%, $p < 0.01$) compared with the controls. The prevalence of atrophic gastritis was lower in EoE patients than in the controls (20.0% vs. 33.3%, $p < 0.05$).

Conclusion: The prevalence of EoE in the Japanese population was 0.051% which was comparable with previous reports in Japan. History of allergies and the absence of atrophic gastritis were associated with EoE.

Keywords: Case-control study; Eosinophilic esophagitis; *Helicobacter pylori*; Japan

Tomoari Kamada <https://orcid.org/0000-0001-6195-2513>Hirofumi Kawamoto <https://orcid.org/0000-0002-9650-3555>**Conflict of Interest**

The authors have no financial conflicts of interest.

Author Contributions

Conceptualization: Ken Haruma. Data curation: Kazumi Imamura, Hiroshi Matsumoto, Yasuhiko Maruyama, Maki Ayaki, Shuhei Tazaki, Nobumi Hisamoto. Formal analysis: Noriaki Manabe. Funding acquisition: Ken Haruma. Methodology: Ken Haruma. Project administration: Hirofumi Kawamoto. Visualization: Tomoari Kamada. Writing - original draft: Kazumi Imamura. Writing - review & editing: Ken Haruma.

INTRODUCTION

Eosinophilic esophagitis (EoE) is an allergy-associated chronic inflammatory condition characterized by the accumulation of eosinophils in the esophagus [1]. This illness can cause obstruction-related symptoms, such as dysphagia and food impaction. The etiology of EoE is currently being clarified and food allergies may be a cause of EoE pathogenesis [2]. It is well described that several risk factors are associated with the development of this disease, which includes sex (male predominance), race (Caucasian), and other allergic conditions (asthma, seasonal rhinitis, and atopic dermatitis) [3]. The incidence and prevalence of EoE have been increasing, and its clinical features have been extensively investigated, especially in Western countries [4].

On the other hand, in Japan, EoE has been poorly acknowledged by general clinicians. The first case of EoE in Japan was reported in English in 2006 [5], although another group reported a case of EoE in Japanese literature in 1998 [6]. But in the past decade, it is recognized that the prevalence of EoE is increasing in Japan [7, 8]. A prospective, multicenter study in 2011 reported that the prevalence of EoE in Japan was 0.02% [9]. Of note, the prevalence appears to be rapidly increasing, and a more recent report indicated the prevalence to be nearly 0.4% in the Japanese population [10]. The low prevalence of EoE in Japan may be in part due to a lack of awareness of the illness.

More study is still needed to determine the exact prevalence of EoE in Japan. Therefore, in the present study, we assessed the incidence of EoE in our related clinical institutes in Japan, as well as the clinical features associated with the disease.

MATERIALS AND METHODS

We conducted a multicenter, retrospective case-control study. A search was made of endoscopic databases in 9 Japanese clinical institutes to identify all diagnosed cases during the period from January 2012 to October 2018. The clinical institutes contained 1 university hospital, 5 general hospitals, and 3 clinics, which were located in Hiroshima, Okayama, Kagawa, Shizuoka, and Tokyo in Japan. In many previous studies, EoE was diagnosed by international consensus criteria which include symptoms of esophageal dysfunction and esophageal biopsy findings [11, 12]. However, in the present study, to avoid underestimating the prevalence of EoE in Japan, we defined a diagnosis of EoE solely based on a biopsy finding of esophageal mucosal eosinophilia of at least 15 eosinophils per high-power field. Patients with neoplasia, peptic ulcers, inflammatory bowel disease, fungal esophagitis, eosinophilic gastroenteritis, and other systemic diseases with eosinophilia were excluded. Ultimately, 66 cases with EoE were diagnosed for further analysis, and a total of 186 age- and sex-matched controls without EoE were chosen. The clinical characteristics and endoscopic patterns were investigated. This study was approved by the institutional ethics committee (no.137) at Public Mitsugi General Hospital. Data are presented as the number of cases and percentages for categorical data. Statistical analysis for categorical data was performed using Pearson chi-squared test, and *t* test for unpaired quantitative data. A *p* value of <0.05 was considered statistically significant.

RESULTS

We found a total of 66 cases (0.051%) of EoE among 130,013 upper endoscopic examinations. An additional 186 age- and sex-matched controls without EoE were recruited from the same sampling frame to serve as controls. The 2 groups, subjects with and without EoE, were not different in mean age (45.2 years vs. 47.1 years) or male percentage (68.2% vs. 67.7%) (Table 1). Twenty-five patients (37.9%) with EoE were diagnosed by medical check-up endoscopy. Patients with EoE had more symptoms (69.7% vs. 10.8%, $p < 0.01$) such as dysphagia and food impaction, and more allergies (65.2% vs. 23.7%, $p < 0.01$). Patients with symptoms tended to have more allergies compared with asymptomatic patients (70.7% vs. 42.9%). Smoking history was less prevalent in the EoE group (33.9% vs. 48.9%, $p < 0.05$). The 2 groups were not different in drinking habits (58.2% vs. 66.1%). No patients had family histories of EoE. We analyzed the blood eosinophil counts of 45 out of the 66 patients with EoE. Sixteen patients (35.6%) had eosinophilia in peripheral blood.

Our study included 3 patients who were 15 years old or younger. They all had some kinds of allergies including food allergies, atopic dermatitis, or bronchial asthma. All patients less than 30 years old (9 of 66, 13.6%) had allergic diseases.

The endoscopic characteristics of EoE have been described previously, such as linear furrows, concentric rings, and whitish exudates [7, 13]. In this study, linear furrows, esophageal rings, and whitish exudates were observed in 87.9%, 81.8%, and 63.6% of patients with EoE, respectively (Table 2). In contrast, such findings were rarely seen in the control group.

Table 1. Clinical characteristics of surveyed patients with EoE

| Characteristic | EoE (n = 66) | Controls (n = 186) |
|---|--------------|--------------------|
| Male sex | 45 (68.2) | 126 (67.7) |
| Age (yr), mean (range) | 45.2 (7–79) | 47.1 (25–78) |
| Symptoms (duplicate count) | 46 (69.7)** | 20 (10.8) |
| Dysphagia/food impaction | 18 (27.3)** | 0 (0) |
| Heartburn | 16 (24.2)** | 7 (3.8) |
| Epigastric pain | 7 (10.6) | 12 (6.5) |
| Presence of allergic diseases (duplicate culture) | 43 (65.2)** | 44 (23.7) |
| Allergic rhinitis | 19 (28.8)** | 20 (10.8) |
| Food allergy | 15 (22.7)** | 11 (5.9) |
| Asthma | 11 (16.7)** | 6 (3.2) |
| Smoking history | 19 (33.9)*,† | 91 (48.9) |
| Drinking habits | 32 (58.2)‡ | 123 (66.1) |

Values are presented as number (%) unless otherwise indicated.

EoE, eosinophilic esophagitis.

†Six unknown cases were excluded. ‡Seven unknown cases were excluded.

* $P < 0.05$ versus controls. ** $P < 0.01$ versus controls.

Table 2. Endoscopic features and *Helicobacter pylori* infection status of surveyed patients with EoE

| Variable | EoE (n = 66) | Controls (n = 186) |
|--------------------------------------|--------------|--------------------|
| Linear furrows | 58 (87.9)** | 1 (0.5) |
| Concentric rings | 54 (81.8)** | 1 (0.5) |
| Whitish exudates | 42 (63.6)** | 0 (0) |
| Reflux esophagitis | 16 (24.2) | 34 (18.3) |
| Atrophic change of gastric mucosa | 13 (20.0)*,† | 62 (33.3) |
| <i>Helicobacter pylori</i> infection | 7 (10.6)† | 34 (18.3)‡ |

Values are presented as number (%).

EoE, eosinophilic esophagitis.

†One unknown case was excluded. ‡Three unknown cases were excluded.

* $P < 0.05$ versus controls. ** $P < 0.01$ versus controls.

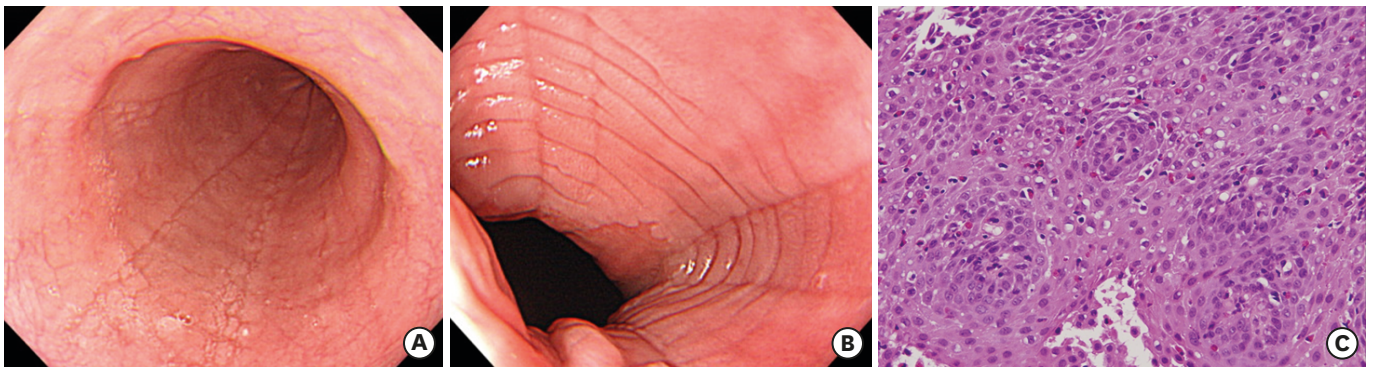


Fig. 1. Endoscopic and histological findings of patients with eosinophilic esophagitis (EoE). Representative endoscopic images of EoE showing linear furrows, whitish exudates (A), and rings (B). Histological findings in a biopsy from the lower-esophagus showing eosinophilic infiltration (C; H&E stain, $\times 100$).

Representative endoscopic and histological findings of patients with EoE are shown in **Fig. 1**. There was no difference in the frequency of reflux esophagitis in the EoE and control groups (24.2% vs. 18.3%).

A recent study has suggested that *Helicobacter pylori* infection is inversely associated with EoE [14]. In the present study, atrophic change in the gastric mucosa, suggesting possible *H. pylori* infection, was found less frequently in the EoE group (20.0% vs. 33.3%, $p < 0.05$). *H. pylori* infection proven by serological test, breath test, or endoscopic biopsy was found in 7 of the 66 EoE cases (10.6%). *H. pylori*-eradicated cases were 12.1% of the EoE group.

We further analyzed the treatment and prognosis of 55 out of the 66 patients with EoE. Thirty-two patients (78.0%) received proton pump inhibitors with or without swallowed topical corticosteroids. During the follow-up period (mean, 23 months), no patient got worse regarding clinical and endoscopic findings. In 14 asymptomatic patients analyzed, 6 patients were treated with proton pump inhibitors or H_2 -blockers, and 8 patients were followed with yearly endoscopy without any treatment.

DISCUSSION

In the present study, we found a total of 66 cases (0.051%) of EoE out of 130,013 upper endoscopic examinations during the period from 2012 to 2018 in Japan. Although the exact reasons are still unclear, EoE is a much rarer disease in Japan compared with Western countries [15]. However, since the recognition of EoE in Japan, the prevalence of this disease has been increasing in the last decade presumably caused by a higher awareness among endoscopic physicians. The prevalence of EoE in Japan is 0.02%–0.4% according to reports published from 2011 to 2018 [9, 10, 16]. Therefore, the prevalence of EoE in our study population is within the same range as the previous reports.

To avoid underestimating the prevalence of EoE in Japan in this study, we defined a diagnosis of EoE solely based on a biopsy finding of esophageal mucosal eosinophilia of at least 15 eosinophils per high-power field. This allowed us to count asymptomatic and presumably relatively mild cases of EoE. Indeed, 30.3% of the EoE cases in this study were asymptomatic (**Table 1**). Even including asymptomatic cases, the prevalence of EoE was found to be just 0.051%, which indicates that this illness is still rare in Japan.

A similar epidemiologic study was recently published by another Japanese research group [16]. In that study, they diagnosed EoE based on esophageal biopsies and reported that the prevalence was 0.20%, which was higher than in our study. However, they found 17 cases of EoE among only 8,589 upper endoscopic examinations in just a single clinical institute. The present study analyzed larger numbers of cases (130,013 cases) from 9 clinical institutes which showed that the prevalence of EoE is 0.051% in Japan.

A previous report on the clinical characteristics of Japanese EoE patients indicated the male/female ratio was 3.3:1 with male preponderance [7]. In the present study, the male/female ratio for EoE was 2.14:1 showing the disease had more male patients but not a biased sex ratio. It was consistent with the fact that approximately 60%–70% of patients had some history of allergic diseases. Smoking history was lower in the EoE group in our study, which is also supported by a previous study [17]. Although the possible mechanism by which the smoking history is lower in EoE is unclear, it could be postulated that nicotine might affect either mucosal infiltration or function of eosinophils. Of interest, it has been reported that nicotine has a positive influence on some inflammatory diseases, including ulcerative colitis [18]. Smoking may suppress the onset or ameliorate the disease progress of EoE through the anti-inflammatory effects of nicotine.

Of note, a previous study suggested an inverse association between *H. pylori* infection and EoE [14]. A subsequent case-control study also showed the possible influence of *H. pylori* infection on EoE in Japanese patients [19]. In the present study, atrophic changes in the gastric mucosa, suggesting possible *H. pylori* infection [20], was seen in 20.0% of the patients with EoE, which was significantly less than in the age- and sex-matched controls (33.3%). However, the difference is too small to be conclusive. It is still unclear whether exposure to *H. pylori* infection has a protective role like that in bronchial asthma [21, 22]. Further studies involving a large population should be performed to determine the association between *H. pylori* infection and allergic disorders, including EoE.

In conclusion, the present study identified 66 Japanese cases (0.051%) of EoE from 130,013 upper endoscopic examinations. History of allergies and the absence of atrophic gastritis were associated with EoE. EoE is a disease which can cause dysphasia by the obstruction of the esophagus. In our study, 30% of the patients were asymptomatic and the rest had mild symptoms. A long-term follow-up study is required to clarify the prognosis.

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