

ORIGINAL ARTICLE

CLINICAL FEATURES OF EOSINOPHILIC ESOPHAGITIS:
TEN JAPANESE CASESYUICHIRO TOMOMATSU, JUNJI YOSHINO, KAZUO INUI, TAKAO WAKABAYASHI, TAKASHI KOBAYASHI,
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School of Medicine, Nagoya, Japan***Aim:** We studied eosinophilic esophagitis (EE) to clarify the clinical and endoscopic features of a Japanese case series.**Methods:** Records of 10 patients diagnosed with EE at our hospital between May 2010 and December 2011 were examined for age, sex, symptoms, allergic disorder, endoscopic findings, and treatment received. Esophageal wall thickness was measured by endoscopic ultrasonography (EUS).**Results:** Patients were seven males and three females with a mean age of 48 years. Symptoms included dysphagia, heartburn, food impaction, and chest pain. Nine patients had a history of allergic diseases. Increased peripheral eosinophil count was observed in one patient whereas increased immunoglobulin E level was observed in eight patients. Endoscopic findings included longitudinal furrows in all patients, mucosal edema in nine patients, loss of vascular pattern in nine patients, white exudates in six patients, cobblestone-like appearance in five patients, and concentric rings in three patients. EUS revealed thickening of the esophageal wall in one patient. Histopathological examination revealed eosinophilic infiltration (≥ 15 eosinophils/high-powered field) in the esophageal epithelium of all patients. Treatment was required in six patients. Proton pump inhibitor (PPI) therapy was given as the first-line treatment but was ineffective in four patients and effective in two patients. Steroid therapy was given to three patients unresponsive to PPI therapy and was effective.**Conclusions:** EE was common among relatively young men and was associated with allergic diseases. Longitudinal furrows were observed as the most characteristic endoscopic finding. Esophageal wall thickening was not commonly observed by EUS.**Key words:** endoscopic findings, eosinophilic esophagitis, longitudinal furrows.

INTRODUCTION

Eosinophilic esophagitis (EE) is a rare allergic disease characterized by eosinophilic infiltration of the esophageal epithelium induced by dietary and airborne antigens. This disease was first reported by Landres *et al.*¹ in 1978, and the first Japanese case was reported by Furuta *et al.*² in 2006. EE was previously recognized as common among children, but it has recently been reported sporadically, but increasingly, in adults.^{3,4} In Western countries, the prevalence of EE is increasing rapidly. A Swiss group (Straumann and Simon) reported that the prevalence of EE was 2/100 000 in 1989 and increased to 23/100 000 in 2004.⁵ A US group (Prasad *et al.*) reported that the prevalence of EE had rapidly increased over the past 30 years until reaching 55/100 000 in 2006.³ In Japan, the prevalence was reported as 17.1/100 000 by Fujishiro *et al.*⁶ in 2011. EE is thought to be rare in Japan, and only 47 Japanese cases have been reported to date. Case data were collected from our cases and from the databases of the Japan Medical Abstracts Society and Pub Med from 2006 to 2011. The present article describes the clinical and endoscopic characteristics of 10 EE cases experienced at our hospital.

METHODS

The records of 10 patients diagnosed with EE at our hospital between May 2010 and December 2011 were examined for age, sex, symptoms, allergic disease, peripheral eosinophil count, immunoglobulin E (IgE) level, endoscopic findings, and treatment received. EE was diagnosed on the basis of esophagus-related clinical symptoms, specific endoscopic findings, such as longitudinal furrows, and eosinophilic infiltration of esophageal epithelium (≥ 15 eosinophils/high-powered field [HPF]), as well as the absence of eosinophilic infiltration in the stomach or duodenum. As eosinophilic infiltration of the esophageal epithelium is an important pathological finding for diagnosing EE, tissue biopsies were collected from multiple sites throughout the esophagus. In this study, a histological finding of ≥ 15 eosinophils/HPF, as recommended by the American Gastrointestinal Association (AGA), was used as the criterion for diagnosing eosinophilic infiltration.⁵ The criterion of ≥ 20 eosinophils/HPF described by Furuta *et al.*² was used as an additional diagnostic criterion. Endoscopic ultrasonography (EUS) was used to measure the thickness of the first through the third layers, consisting of mucosa and submucosa (m + sm), and that of the fourth layer, consisting of the muscularis propria (mp). The m + sm and mp thicknesses of the normal esophageal wall in another 20 patients (controls) were used as comparative parameters for identifying esophageal wall thickening in EE patients. In the controls, EUS was carried out for

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Received 16 January 2012; accepted 27 April 2012.

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esophageal submucosal tumor (SMT) in 11 patients, early esophageal cancer in six patients, and gastric cancer in three patients. The controls had a mean age of 60 years (range 34–80 years) and consisted of 16 males and four females. The measurement of esophageal wall by EUS performed normal esophageal wall in cases of esophageal SMT and cancer. For endoscopy, Olympus GIF260 and 240Z endoscopes (Olympus Corp., Tokyo, Japan) were used. For EUS, 20-MHz and 12-MHz narrow ultrasound probes (UM-2R and UM-3R; Olympus Corp., Tokyo, Japan) were used. Statistical analysis of EUS findings was carried out using the *t*-test.

RESULTS

During the study period of 19 months (from May 2010 to December 2011), upper gastrointestinal endoscopy was carried out in 7557 patients (mean age of 59 years, 4764 males [63%], and 2793 females [37%]). The prevalence of EE was calculated to be 132.3/100 000 in our institution. The EE patients had a mean age of 48 years (range 26–73 years): 30 years or younger in one patient, 31–40 years in three patients, 41–50 years in two patients, 51–60 years in two patients, 61–70 years in one patient, and 71 years or older in one patient. The patients of EE consisted of seven males (70%) and three females (30%), indicating a high prevalence among relatively young men. Of the symptoms, dysphagia, the most common symptom, was reported by four patients (40%), followed by heartburn reported by three patients (30%), food impaction reported by two patients (20%), and chest pain reported by one patient (10%). Nine patients (90%) had allergic diseases, including three patients with bronchial asthma, three with allergic rhinitis, two with urticaria, one with atopic dermatitis, one with food allergy, and one with drug-induced allergy, with some patients suffering from multiple allergic conditions. Blood biochemistry tests showed a mean peripheral eosinophil count of 303/ μ L (138–595/ μ L), with only one (10%) patient having more than 500 eosinophils/ μ L. The mean IgE level was 541.2 IU/mL (2.5–2332.0 IU/mL), with eight (80%) patients showing increased IgE (Table 1). Upper gastrointestinal endoscopy revealed several longitudinal furrows coursing along the long axis of the esophagus throughout the organ in all 10 patients. These longitudinal furrows were more clearly visualized by adjusting the air volume to deflate the esophagus (Fig. 1a,b). Abnormal mucosal findings included mucosal edema in nine

(90%) patients and loss of vascular pattern in nine (90%) patients (Fig. 1c). Other characteristic findings included white exudates in six (60%) patients (Fig. 1d), cobblestone-like appearance in five (50%) patients (Fig. 1e), and concentric rings wider than the normal crease pattern in three (30%) patients (Fig. 1f) (Table 2). EUS to measure esophageal wall thickness was carried out in all patients, showing a mean m + sm thickness of 1.9 ± 1.6 mm (1.2–6.3 mm) and mean mp thickness of 1.5 ± 0.3 mm (1.2–1.9 mm) in EE patients. No significant difference was found in esophageal wall thickness between EE patients and the controls with respect to m + sm (1.9 ± 1.6 mm vs 1.4 ± 0.4 mm, $P = 0.33$) or mp (1.5 ± 0.3 mm vs 1.4 ± 0.4 mm, $P = 0.62$) thickness (Table 3). One patient (Case 4) was found to have marked thickening of the esophageal wall by EUS with a m + sm thickness of 6.3 mm. Pathological findings revealed mucosal edema in biopsy samples obtained from the sites of esophageal wall thickening identified by EUS (Fig. 2a,b). In four control cases, the pathological findings were evaluated. They had no inflammatory changes such as mucosal edema (Fig. 2c,d). Magnifying endoscopy with narrow band imaging (NBI) to evaluate vascular changes of EE was carried out in four patients and revealed unclear intraepithelial papillary capillary loop (IPCL) in two patients (Fig. 3). In the biopsy, an average of 3.6 (2–5) samples was collected from the upper to the lower portions of the esophagus. Histopathological examination revealed eosinophilic infiltration of the esophageal epithelium (≥ 15 eosinophils/HPF) in all patients (Fig. 4a,b). Of them, eight (80%) patients had 20 or more eosinophils/HPF. Meanwhile, neither gastric nor duodenal biopsy revealed eosinophilic infiltration in any patients. Other pathological findings included eosinophilic microabscess, defined as an aggregate of four or more eosinophils (Fig. 4c,d). Esophagography was carried out in seven patients and revealed favorable extension of the esophageal wall in all seven patients and light linear barium spots aligned along the long axis of the esophagus in three patients (Fig. 5).

Treatment was required in six (60%) patients, with initial treatment consisting of oral proton pump inhibitor (PPI). PPI therapy was effective in two patients, whereas the remaining four patients showed no improvement in symptoms after at least 5 weeks of oral PPI therapy. Three of the four patients unresponsive to PPI were also treated with an oral steroid (prednisolone 20 mg/day), which resulted in improved symp-

Table 1. Characteristics of 10 cases of eosinophilic esophagitis

Case	Age (years)	Sex	Symptom	Allergic disease	Peripheral eosinophil count (/ μ L)	IgE (IU/mL)
1	40	M	Dysphagia	Urticaria	138	39.2
2	51	M	Dysphagia	Bronchial asthma	208	2.5
3	46	F	Chest pain	None	304	252.8
4	26	M	Heartburn	Bronchial asthma/Food allergy	451	1487.0
5	39	F	Food impaction	Allergic rhinitis	246	194.5
6	66	M	Dysphagia	Drug allergy	348	523.0
7	73	M	Dysphagia	Urticaria	376	186.0
8	52	M	Food impaction	Atopic dermatitis	170	2332.0
9	36	M	Heartburn	Allergic rhinitis	595	200.6
10	46	F	Heartburn	Bronchial asthma/Allergic rhinitis	195	194.4

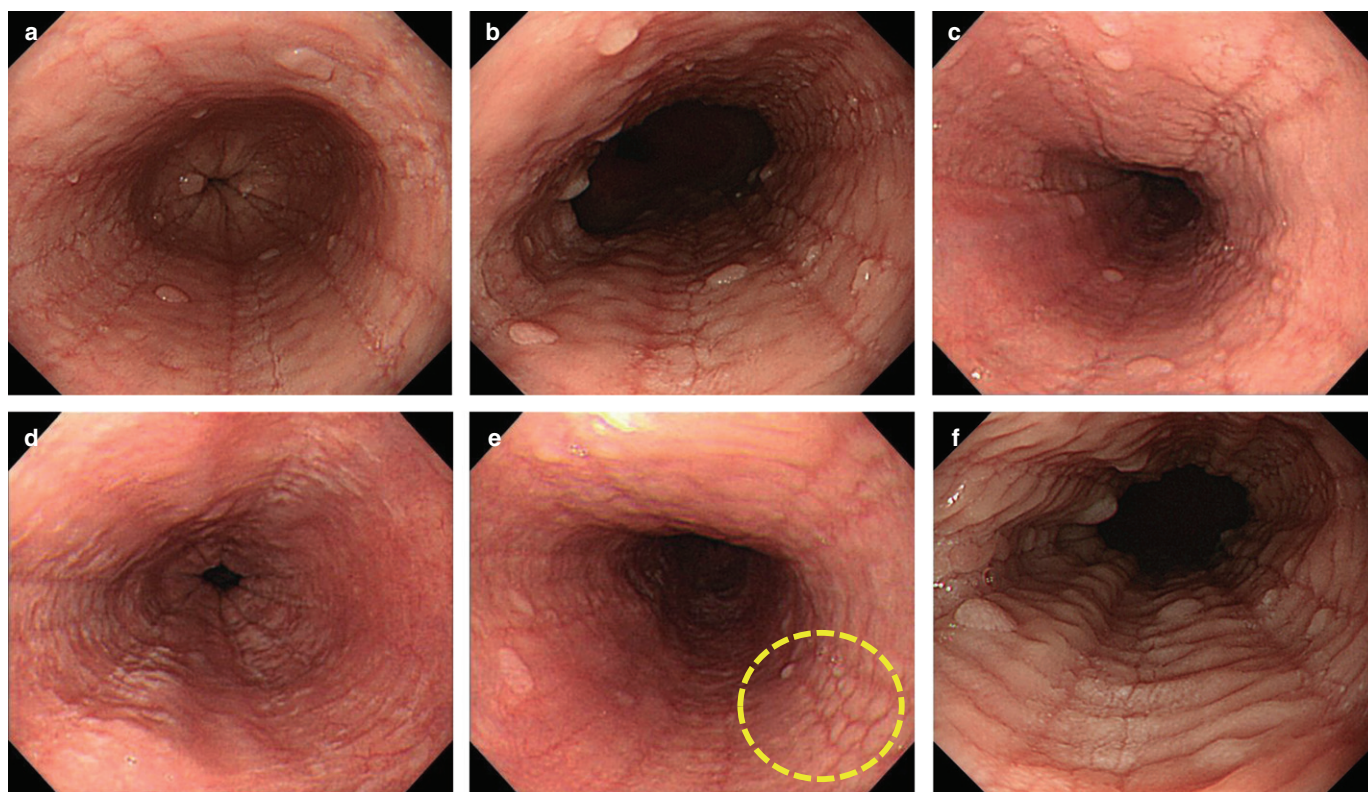


Fig. 1. Findings of upper gastrointestinal endoscopy. (a),(b) Longitudinal furrows (Case 2). Images obtained from a 51-year-old man. Several longitudinal furrows coursing along the long axis of the esophagus are observed throughout the organ. These longitudinal furrows are more clearly visualized by adjusting the air volume to deflate the esophagus. (c) Mucosal edema and loss of vascular pattern (Case 1). Image obtained from a 40-year-old man. The esophageal mucosa is whitish, thickened, and edematous, with a loss of vascular pattern. (d) White exudates (Case 1). Image obtained from a 40-year-old man. White exudates smaller than those observed in *Candida* esophagitis are present all over the esophageal epithelium. (e) Cobblestone-like appearance (Case 1). Image obtained from a 40-year-old man. Cobblestone-like appearance is present in the area surrounded by a dotted line. (f) Concentric rings (Case 2). Image obtained from a 51-year-old man showing concentric rings wider than the normal crease pattern.

Table 2. Endoscopic findings of 10 cases of eosinophilic esophagitis

Endoscopic findings	<i>n</i> = 10 (%)
Longitudinal furrows	10 (100)
Mucosal edema	9 (90)
Loss of vascular pattern	9 (90)
White exudates	6 (60)
Cobblestone-like appearance	5 (50)
Concentric rings	3 (30)

toms and endoscopic findings. The remaining one patient was observed without steroid use because his symptoms did not worsen compared with those prior to PPI therapy (Table 4).

DISCUSSION

Eosinophilic esophagitis is an allergic disease characterized by eosinophilic infiltration of the esophageal epithelium induced by dietary and airborne antigens.^{7,8} Once stimulated and activated by antigenic droplets, T-helper cells (Th2) in the esophageal epithelium produce interleukin (IL)-5 and IL-13. Eotaxin 3, produced following stimulation by IL-13,

Table 3. Thickness of the esophagus wall in patients with eosinophilic esophagitis and controls

	EE patients <i>n</i> = 10	Controls <i>n</i> = 20	<i>P</i> -value
m and sm ($\pm$ SD, mm)	1.9 $\pm$ 1.6	1.4 $\pm$ 0.4	0.33
mp ($\pm$ SD, mm)	1.5 $\pm$ 0.3	1.4 $\pm$ 0.4	0.62

EE, eosinophilic esophagitis; m, mucosa; mp, muscularis propria; sm, submucosa.

and IL-5 induce an increase of eosinophils, causing chronic inflammation involving eosinophils in the esophageal epithelium, which is suggested to contribute to the pathogenesis of EE.^{9,10} Increased eosinophils in the esophagus are observed in not only EE, but also in reflux esophagitis, Crohn's disease, collagen diseases, infectious esophagitis (e.g. *Candida* esophagitis), drug-induced esophagitis, and eosinophilic gastroenteropathy.¹¹ In reflux esophagitis, eosinophilic infiltration is observed primarily in the lower esophagus with a histological finding of 3–4 eosinophils/HPF.¹² In comparison, eosinophilic infiltration in EE is observed throughout the esophagus, with a substantially higher number of eosinophils observed histologically (15 eosinophils/HPF). The degree of eosinophilic

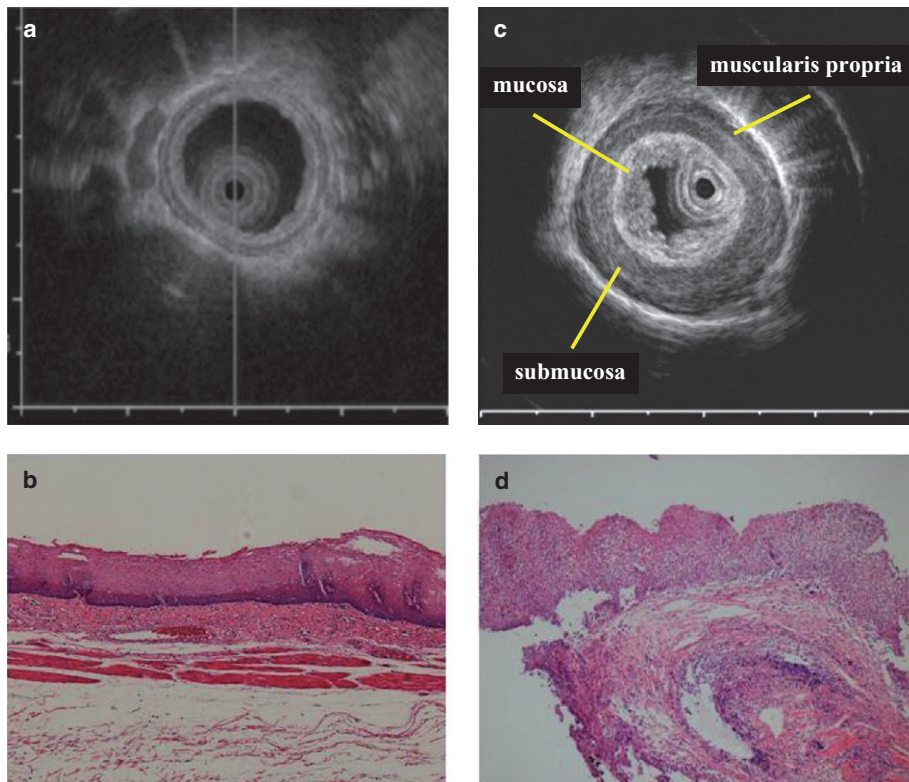


Fig. 2. Endoscopic ultrasonography (EUS) and pathological findings of the esophageal wall. (a) EUS image obtained from a control patient (65-year-old man). Esophageal wall thickening is not observed, with a mucosal plus submucosal layer thickness of 1.3 mm. (b) Low magnification image ($\times 10$) of the same control patient is shown. The control case has no inflammatory changes such as mucosal edema. (c) EUS image obtained from a 26-year-old man (Case 4). Esophageal wall thickening is observed, with a mucosal plus submucosal layer thickness of 6.3 mm in some parts of the esophagus. (d) Low magnification image ($\times 10$) of Case 4 is shown. Pathological examination of biopsy samples obtained from the sites of thickening identified by EUS reveals edematous change and eosinophilic infiltration of the mucosal epithelium and lamina propria.

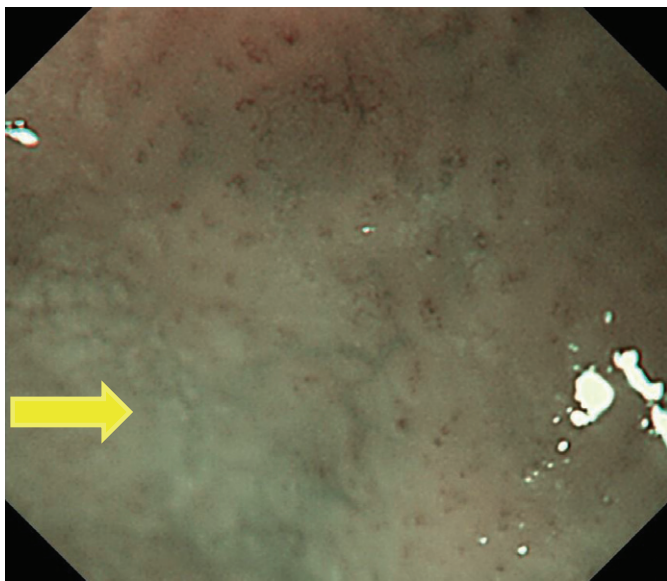


Fig. 3. Findings of magnifying endoscopy with narrow band imaging (Case 2). Magnifying images obtained from a 51-year-old man. Intraepithelial papillary capillary loop is unclear (arrow).

infiltration of the esophageal epithelium varies among reports. For example, some studies required ≥ 15 eosinophils/HPF⁵ whereas others required ≥ 20 eosinophils/HPF.²

The prevalence of EE (132.3/100 000) in the present study was higher than that of other reports (17.1–55/100 000).^{3,5,6} The high prevalence of this study caused that we performed actively multiple esophageal biopsies, when the EE-specific

findings such as longitudinal furrows was observed. The mean age of EE patients in Western countries has been reported as 38 years, with males accounting for 76% of all patients,¹³ while the mean age and proportion of men in Japanese EE patients are reported to be 47 years and 75%, respectively.¹⁴ A similar trend was observed in the present study, with a mean age of 48 years and male patients accounting for 70% of all included patients, confirming the high prevalence of EE among relatively young men. Dysphagia and food impaction are the most common symptoms of EE, followed by gastroesophageal reflux disease-like symptoms such as heartburn, chest pain, and abdominal pain.^{15–18} In the present study, dysphagia and food impaction accounted for more than half of all symptoms reported. The persistence of chronic inflammation is considered to lead to fibrosis under the lining of the esophagus, causing such symptoms as dysphagia and food impaction.

EE is commonly associated with allergic disease;¹⁹ 90% of the patients in the present study also had a history of allergic disease. The peripheral eosinophil count in EE patients has been reported to show a 10–50% increase in adults and a 20–100% increase in children.¹⁵ A previous study suggested an association between increased peripheral eosinophil count and dysphagia,²⁰ whereas another study showed correlation between the degree of increased eosinophils and the severity of EE.²¹ Increased IgE level has been observed in 60–69% of adult EE and 71–78% of pediatric EE patients.¹⁵ In the present study, an increased peripheral eosinophil count was observed in 10% of the patients, whereas an increased IgE level was observed in 80% of the patients.

Endoscopic findings of EE include longitudinal furrows, concentric rings, white exudates, cobblestone-like appearance, edema, and loss of vascular pattern.^{15,22} Meanwhile, it has also been suggested that no abnormal findings can be

Fig. 4. Pathological findings of biopsy specimens. (a),(b) Eosinophilic infiltration (Case 3). Intermediate and high magnification images (×20, ×40) are shown. These images are obtained from a 46-year-old woman. Marked eosinophilic infiltration (≥15 eosinophils/HPF) is observed in the esophageal epithelium. (c),(d) Eosinophilic microabscess (Case 7). Intermediate and high magnification images (×20, ×40) are shown. These images are obtained from a 73-year-old man and show eosinophilic microabscesses (arrow) consisting of many eosinophils.

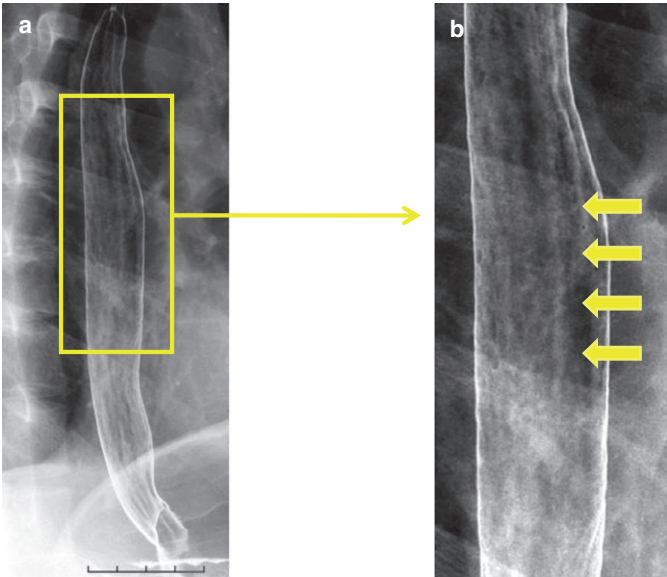
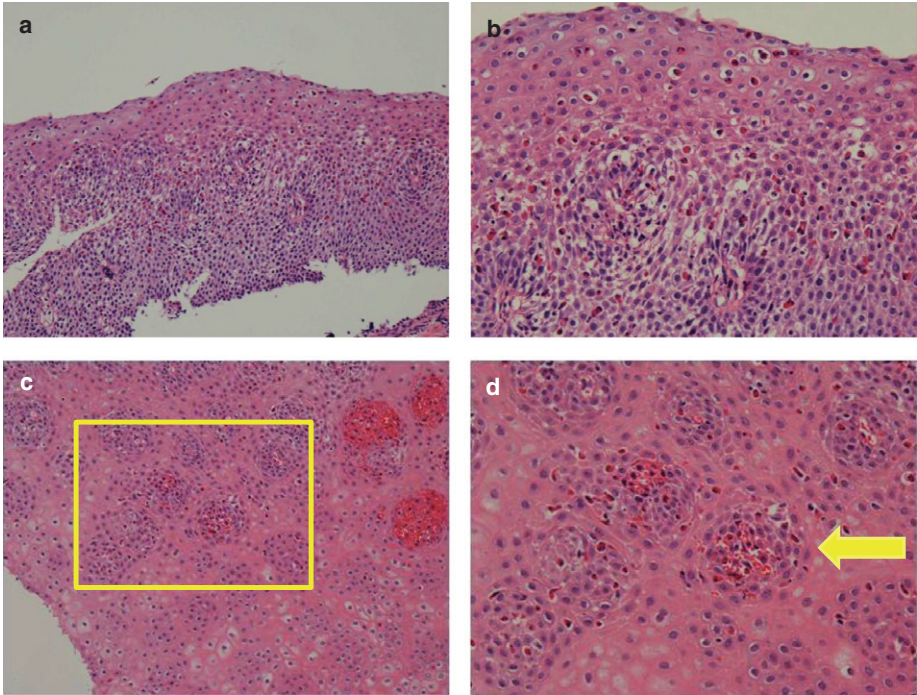


Fig. 5. Barium esophagogram (Case 1). (a),(b) Images obtained from a 40-year-old man. The esophageal wall is well extended. Linear light barium spots (arrow) are observed along the long axis of the esophagus.

detected by endoscopy in 24.8% of all EE patients.²² In the present study, longitudinal furrows were observed in all patients on endoscopy and were thus considered the most characteristic finding of EE. While the mechanism of how longitudinal furrows and cobblestone-like appearance occur is unknown, white exudates are known to consist of eosinophilic microabscesses, defined as an aggregate of four or more eosinophils.²³ Considering the definition of white exudates, they can be used as an indicator of eosinophilic infiltration into the esophageal epithelium, and carrying out

Table 4. Treatment of 10 cases of eosinophilic esophagitis

Case	Age (years)	Sex	Treatment
1	40	M	PPI not effective, PSL effective
2	51	M	PPI not effective, PSL effective
3	46	F	PPI not effective, PSL effective
4	26	M	PPI not effective
5	39	F	None
6	66	M	None
7	73	M	None
8	52	M	None
9	36	M	PPI effective
10	46	F	PPI effective

PPI, proton pump inhibitor; PSL, prednisolone.

biopsy on white exudates is an effective approach for diagnosing EE. Concentric rings are thought to be formed as a result of thickening of the submucosal layer and scar contracture due to chronic inflammation.

Longitudinal furrows are recognized as light linear barium spots aligned along the long axis of the esophagus on esophagography. This finding was observed in three of the seven (42.9%) patients who underwent esophagography, with no abnormal mucosal finding observed in the remaining four patients. While esophagography failed to clearly visualize EE-specific findings such as longitudinal furrows, endoscopy successfully revealed longitudinal furrows in all patients. This is likely because the longitudinal furrows could be clearly visualized by adjusting the air volume to deflate the esophagus on endoscopy, despite the fact that extension of the esophageal mucosa makes longitudinal furrows unclear.

With the criterion of ≥15 eosinophils/HPF for diagnosing eosinophilic infiltration on esophageal biopsy, Gonsalves *et al.*²⁴ demonstrated that the diagnostic sensitivity with five

biopsies was 100%, whereas that with one biopsy was only 55%. The present study achieved an average of 3.6 biopsies per patient, suggesting the importance of carrying out multiple biopsies when diagnosing EE.

Very few studies have used EUS to examine esophageal thickening in EE. Fox *et al.*²⁵ examined the esophageal wall of 11 pediatric patients with EE by EUS and detected increased thickness of the m + sm layers and that of the mp layer of the esophagus. In the present study, we compared the thickness of the m + sm layers and that of the mp layer between EE patients and controls, and found a marked increase in the m + sm thickness (6.3 mm) in one patient with EE, although no significant difference was found between patients and controls. On biopsy, mucosal edema was found in samples obtained from the sites of thickening identified by EUS. The EUS findings reflected histologically mucosal edema in EE.

Only one Japanese case report of magnifying endoscopic findings of EE reported that IPCL revealed a decrease.²⁶ With inflammatory change of the esophagus, such as in reflux esophagitis, IPCL is recognized as dilatation.²⁷ In the present study, two cases of EE showed unclear IPCL. This change is considered of mucosal edema by eosinophilic infiltration of the esophageal epithelium. These findings may be not helpful for the diagnosis of EE, because the small number of patients with EE performed magnified endoscopy in our study. Further studies with larger number of patients with EE will be necessary to confirm the value of magnifying endoscopic findings.

There are no established treatment guidelines for EE and, although the effectiveness of steroid treatment has been suggested,¹⁵ a consensus has not yet been reached regarding how and for how long such treatment should be given. Because we considered the side-effects of steroid therapy, PPI was selected as the first-line therapy of EE patients in our institution. Also, prednisolone (PSL) was used for patients unresponsive to PPI. In the present study, three patients receiving steroid treatment responded to the therapy, whereas PPI therapy was effective in only two patients. The diagnostic criteria for EE in the USA include no response to high-dose PPI therapy,¹⁵ although several studies have shown the effectiveness of PPI in the treatment of EE.^{14,23,28,29} The reason for the effectiveness of PPI on EE can be assumed as follows. Eotaxin 3, a factor playing an important role in eosinophilic infiltration of the esophageal epithelium, has been shown to increase in number under acidic conditions.³⁰ As PPI prevent gastric juice from regurgitating into the esophagus, the use of PPI may lead to a decreased level of eotaxin 3 and a subsequent decrease in eosinophilic infiltration.

Although EE is a rare condition, it has received increased attention due to the recent increase in its prevalence. The possibility of EE should be considered when treating a patient suffering from esophagus-related symptoms, such as dysphagia and food impaction, and when observing endoscopic findings such as longitudinal furrows, mucosal edema, loss of mucosal vascular pattern, white exudates, cobblestone-like appearance, and concentric rings.

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