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Reversibility of Endoscopic Features after Treatment for Eosinophilic Esophagitis

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Purpose: The prevalence and incidence of eosinophilic esophagitis (EoE) are increasing worldwide. Despite increased understanding of inflammatory pathogenesis, changes in endoscopic features after treatment of EoE have not been clearly described. We aimed to investigate the reversibility of endoscopic features of EoE after treatment.

Materials and Methods: Out of 58 adult subjects who were diagnosed with EoE at the Yonsei University Health System from July 2006 to August 2019, we recruited 33 subjects (30 males; mean age: 42 years) whose pre-treatment and post-treatment endoscopic images were available. Endoscopic features included both inflammatory and fibrostenotic features. Exudate, edema, furrow, and crepe paper-like mucosa were classified as inflammatory features. Ring and stricture were classified as fibrostenotic features. We compared changes in endoscopic features after treatment for EoE.

Results: After treatment, clinical symptoms improved in all patients. The following endoscopic features were observed before treatment: furrow (81.8%), edema (90.9%), exudate (42.4%), ring (27.3%), crepe paper-like mucosa (15.2%), and stricture (3.0%). Endoscopic remission was achieved in 21 patients (63.6%). Inflammatory features were reversible (72.7%, $p<0.001$), whereas fibrostenotic features were not (10%, $p=0.160$). Exudate had resolved in 92.9% of patients, edema in 70% and furrow in 88.9%. Ring and stricture persisted in almost all of the patients (9/10) who had these endoscopic features before treatment.

Conclusion: We outlined the reversibility of endoscopic inflammatory features of EoE. Fibrostenotic features were irreversible after esophageal remodeling in patients with EoE. However, further validation studies with long-term follow-up are needed.

Key Words: Esophagus, eosinophilia, eosinophilic esophagitis

INTRODUCTION

Eosinophilic esophagitis (EoE) is a chronic immune/allergic condition with a multifactorial etiology.[1] EoE was first described in 1978,[2] and pathological entities have been confirmed in reports from 1993 to 1994.[3,4] The prevalence and incidence of EoE are increasing worldwide. According to a recent meta-analysis, the incidence rate was 7.7/100000 person-years in adults, with a prevalence of 42.2 cases per 100000 adults.[5] The most important factors in the diagnosis of EoE are clinical symptoms and histological findings. Some EoE patients have difficulty swallowing, but most show various atypical symptoms, such as vomiting and abdominal pain, or no symptoms.[6,7] Histological diagnosis is confirmed when there are more than 15 eosinophils per high-power field (HPF).[8] EoE exhibits various endoscopic features, such as linear furrows, exudate, fragile mucosa, edema, rings, and strictures,[9] although the reported prevalence of endoscopic features in EoE patients varies among in the literature.[10,11] Although these endoscopic features are important for the diagnosis of EoE, individual features are not sensitive or specific enough to support diagnosis. Recently, an EoE endoscopic reference score (EREFS) has been used to overcome these limitations and to quantify endoscopic fea-

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tures, and good performance has been reported in several studies.[12,13] Several studies using the scoring system reported decreases in scores after EoE treatment, indirectly confirming an observed correlation between EoE activity and endoscopic features.[12,14] However, despite several studies on EoE, the reversibility of endoscopic features after treatment has not been clearly described. In this study, we aimed to investigate the reversibility of endoscopic features of EoE after treatment.

MATERIALS AND METHODS

Study subjects and methods

We reviewed the records of 58 patients who were diagnosed with EoE at two tertiary gastroenterology centers (Gangnam Severance Hospital and Severance Hospital, Yonsei University) from July 2006 to August 2019. Baseline characteristics, including age, sex, patient's symptoms, and endoscopic features, were identified retrospectively. The cut-off value for confirming EoE was more than 15 eosinophils per HPF on esophageal biopsy. In all, 33 patients with identifiable endoscopic images before and after treatment were enrolled in this study. Endoscopy was performed for various causes, including examinations for gastrointestinal symptoms and screening for malignancy. If EoE was suspected, two to four biopsy samples were taken to obtain enough samples. Treatment for EoE comprised the use of a proton-pump inhibitor (PPI) or topical steroids (fluticasone propionate) for 4–8 weeks. Even after PPI treatment, a topical steroid was used if symptoms persisted. Fluticasone was given as two puffs to swallow twice a day. The daily dosage of fluticasone was 1000 mcg. Patients were instructed to puff the fluticasone into their mouth at the same time without deep inhalation or using spacers. During PPI treatment, patients did not follow the six-food elimination diet. After treatment, follow-up endoscopy was performed. This study was approved by the Institutional Review Board of Gangnam Severance Hospital (No. 3-2019-0415).

Endoscopic features

Endoscopic images were captured using standard endoscopes

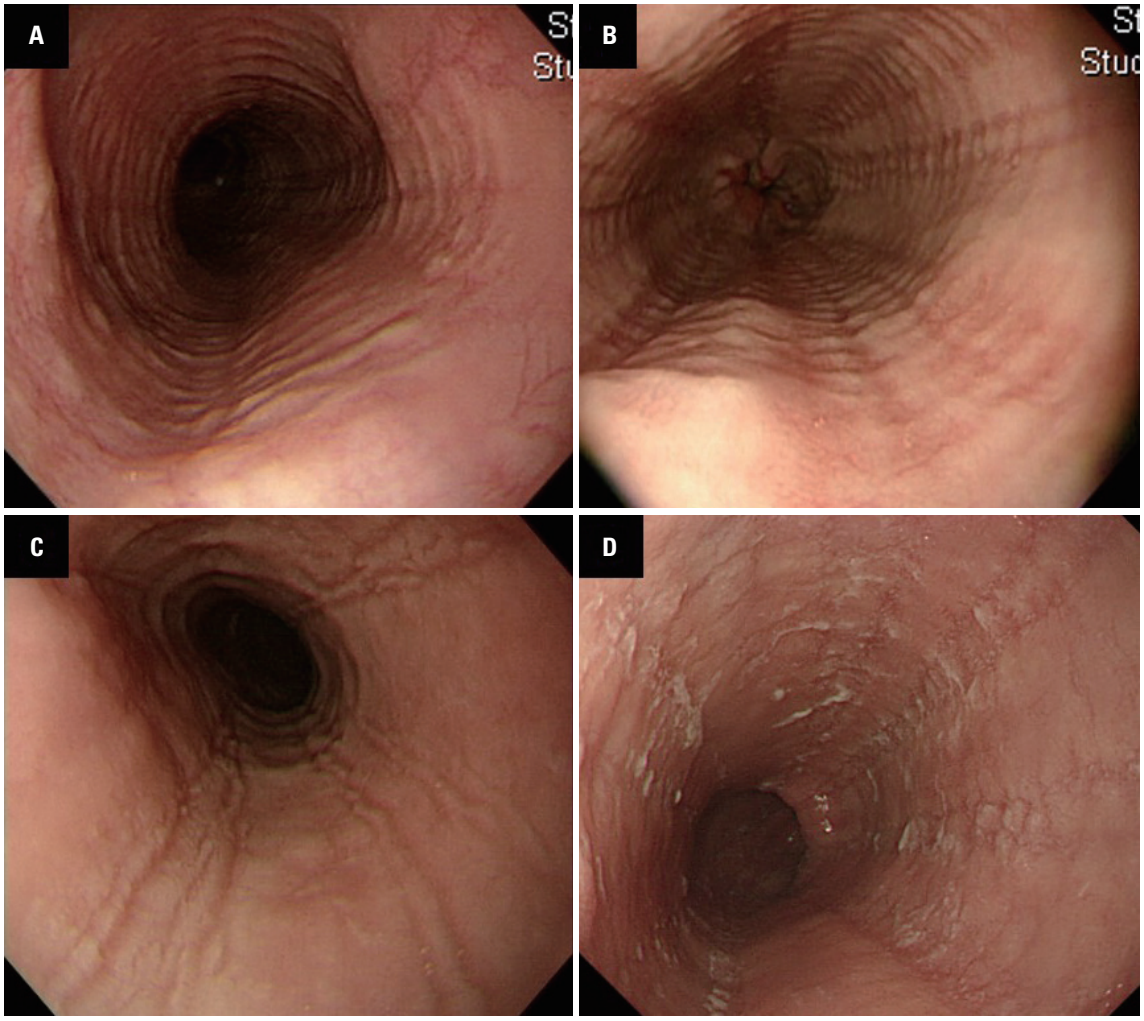

Fig. 1. Typical endoscopic features of eosinophilic esophagitis. (A) Esophageal rings. (B) Rings and linear furrows, as well as mucosal edema. (C) Linear furrows and mucosal edema. (D) Linear furrows and exudates, as well as mucosal edema.

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(GIF-Q260J, GIF-H260, and GIF-H290; Olympus Medical Systems, Co., Ltd., Tokyo, Japan). All endoscopic features and reports were reviewed to confirm the endoscopic features.

Endoscopic features of EoE are presented in Fig. 1. Edema was defined as congested, granular, or abnormally colored esophageal mucosa with the loss of normal vasculature. Exudate was an irregularly distributed white, viscous substance. Furrow referred to longitudinal grooves or crevices parallel to the esophageal long axis, also called linear fissures or tram tracks. Crepe paper-like mucosa referred to esophageal mucosa that had lost elasticity and bleeds easily. Rings referred to a concentric corrugated esophagus, also called as felinization, trachealization, or corrugation. Stricture was defined as a focal narrowing of the esophagus. Inflammatory features included edema, exudate, furrow, and crepe paper-like mucosa. Fibrostenotic features consisted of ring and stricture.

The degree of endoscopic features was recorded according to the EREFS. Edema, crepe paper-like mucosa, and strictures were recorded as absent or present. Mild exudate was defined as less than 10% of the entire esophageal mucosa covered with exudate and severe exudate as more than 10% coverage. Furrows were classified as mild (furrows without visible depth) or severe (furrows with visible depth or mucosal indentation). Rings were classified as mild (circumferential ridges), moderate (distinct rings that do not impair passage of a standard endoscope), and severe (distinct rings that impair passage of a standard endoscope).

Table 1. Baseline Characteristics of the Study Cohort with Eosinophilic Esophagitis

Characteristics	n (%)
Male sex	30 (90.9)
Age (yr) (median, range)	42 (21–66)
Duration of endoscopic surveillance (median, range)	2 (2–12)
Symptoms	
Dysphagia	16 (48.4)
Heart burn	6 (18.2)
Dyspepsia	2 (6.1)
Reflux	2 (6.1)
Asymptomatic	7 (21.2)
Endoscopic features	
Edema	30 (90.9)
Exudate	14 (42.4)
Furrow	27 (81.8)
Crepe paper like mucosa	5 (15.2)
Ring	9 (27.3)
Stricture	1 (3.0)
Treatment	
PPI only	23 (69.7)
PPI+fluticasone (swallowed)	9 (27.3)
PPI+balloon dilatation	1 (3.0)

PPI, proton-pump inhibitor.

Statistical analysis

Chi-squared test and Fisher's exact test were used to analyze categorical variables, and the Wilcoxon signed rank test was used for non-categorical variables. $p<0.05$ indicated statistical significance. All statistical analyses were performed using SPSS version 23.0 (IBM Corp., Armonk, NY, USA).

RESULTS

The baseline characteristics of EoE patients are shown in Table 1. Our study population included 30 male and 3 female patients with a median age of 42 years (range, 21–66). Among 26 symptomatic patients (78.8%), dysphagia was present in 16

Table 2. Endoscopic Features according to Symptom

Endoscopic features	Symptomatic	Asymptomatic	*p* value
Inflammatory feature	26 (100)	7 (100)	-
Edema	23 (88.5)	7 (100)	0.346
Exudate	11 (42.3)	3 (42.9)	0.427
Furrows	21 (80.8)	6 (85.7)	0.624
Crepe paper-like mucosa	5 (19.2)	0 (0)	0.277
Fibrostenotic feature	9 (34.6)	1 (14.3)	0.294
Rings	8 (30.8)	1 (14.3)	0.365
Strictures	1 (3.8)	0 (0)	0.788

Data are presented as n (%).

Table 3. Endoscopic Features Before and After Treatment of Eosinophilic Esophagitis

	Pre-treatment	Post-treatment	*p* value
Inflammatory feature	33 (100)	9 (27.3)	<0.001
Edema	30 (90.9)	9 (27.3)	<0.001
Mild	17	6	
Severe	13	3	
Exudate	14 (42.4)	1 (3.0)	<0.001
Mild	10	1	
Severe	4	0	
Furrows	27 (81.8)	3 (9.1)	<0.001
Mild	16	2	
Severe	11	1	
Crepe paper-like mucosa	5 (15.2)	2 (6.1)	0.083
Fibrostenotic feature	10 (30.3)	9 (27.3)	0.160
Rings	9 (27.3)	8 (24.2)	0.317
Mild	2	1	
Moderate	7	7	
Severe	0	0	
Strictures	1 (3.0)	1 (3.0)	-
Inflammatory EREFS	3.2±1.6	0.6±1.0	<0.001
Fibrostenotic EREFS	0.5±0.8	0.5±0.8	0.317
Total EREFS	3.7±1.8	1.7±1.5	<0.001

EREFS, endoscopic reference score.
Data are presented as n (%) or mean±standard deviation.

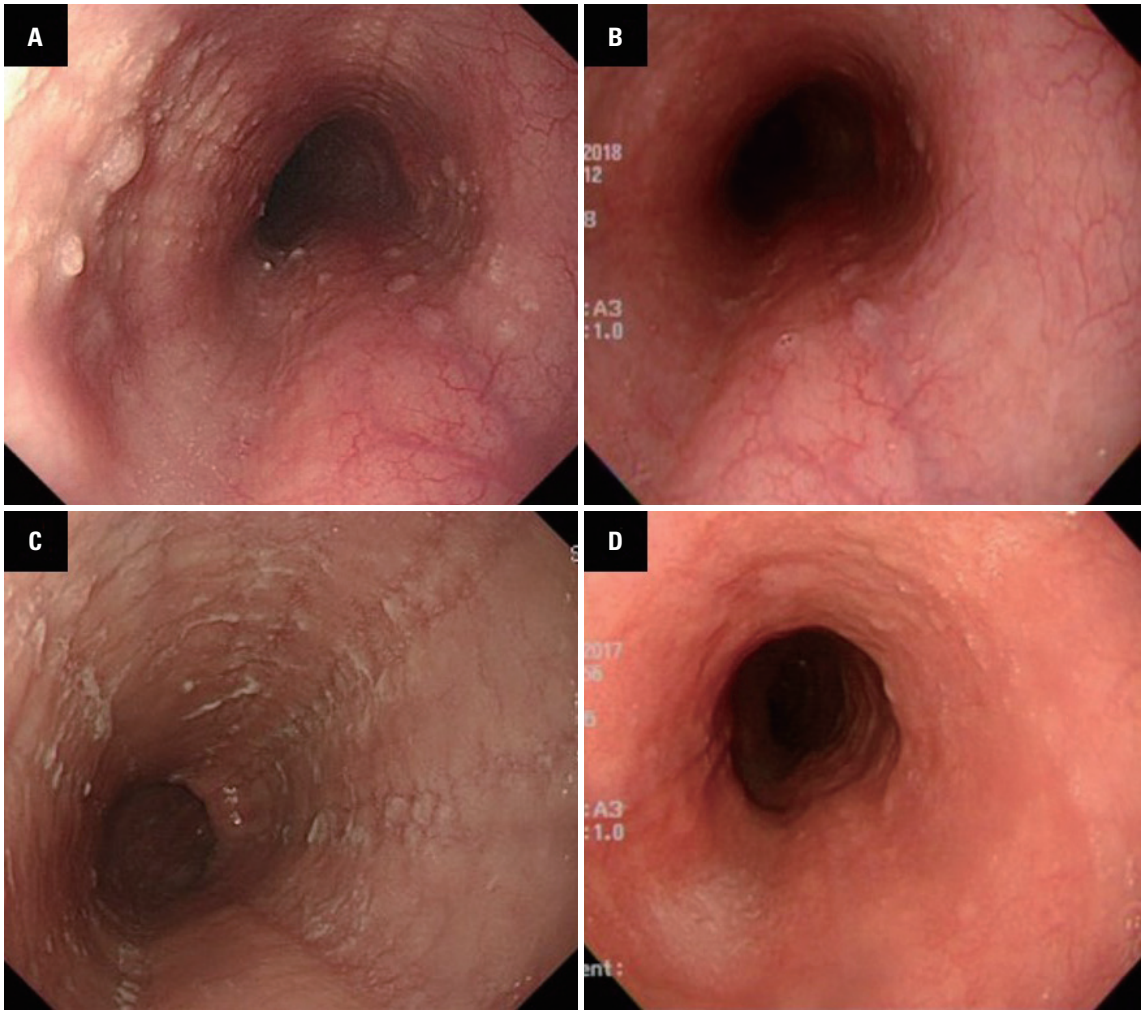

Fig. 2. Representative cases of reversible endoscopic features. (A) Exudate and furrows were identified before treatment in a patient with eosinophilic esophagitis. (B) After 8 weeks of treatment with a proton pump inhibitor, exudate and furrows disappeared. (C) Inflammatory features, including mucosal edema, furrows, and exudate, were identified before treatment in a patient with eosinophilic esophagitis. (D) After treatment, the patient's symptoms and endoscopic features had resolved.

(48.4%), heart burn in 6 (18.2%), dyspepsia in 2 (6.1%), and reflux in 2 (6.1%). Seven patients (21.2%) were asymptomatic and underwent endoscopy for screening and surveillance of gastric cancer. Endoscopic features were not correlated with the patients' symptoms (Table 2). All patients initially received a standard dose of a PPI. In nine patients, symptoms did not improve after 8 weeks of PPI treatment, so they were administered topical steroids; one patient with esophageal stricture underwent balloon dilatation.

The endoscopic features are shown in Table 3. All patients showed inflammatory features on pre-treatment endoscopy: edema was observed in 30 (90.9%), exudate in 14 (42.4%), furrow in 27 (81.8%), and crepe paper-like appearance in 5 (15.2%). Ten patients (30.4%) showed fibrostenotic features in the pre-treatment endoscopy: rings were observed in 9 (27.3%), and strictures in 1 (3.0%). According to the EREFS, findings of exudates and furrows were mild. All inflammatory features showed reversibility, regardless of the degree. Almost all rings were moderate rings and persisted after treatment. Mild rings were observed in two patients, but disappeared after treatment in one patient. All inflammatory features except crepe paper-like mucosa had significantly improved after treatment (p<0.001), whereas fibrostenotic features did not. The mean EREFS of inflammatory features was 3.2. After treatment for EoE, inflammatory EREFS decreased to 0.6 (p<0.001). Total EREFS values significantly decreased after treatment (p<0.001). However, fibrostenotic EREFS did not decrease after treatment (p=0.325). Representative cases of reversible endoscopic features and irreversible endoscopic features are shown in Figs. 2 and 3.

DISCUSSION

Since EoE was recognized in a series of cases 20 years ago,[3,4] there has been much research on it.[15] Currently, several aspects

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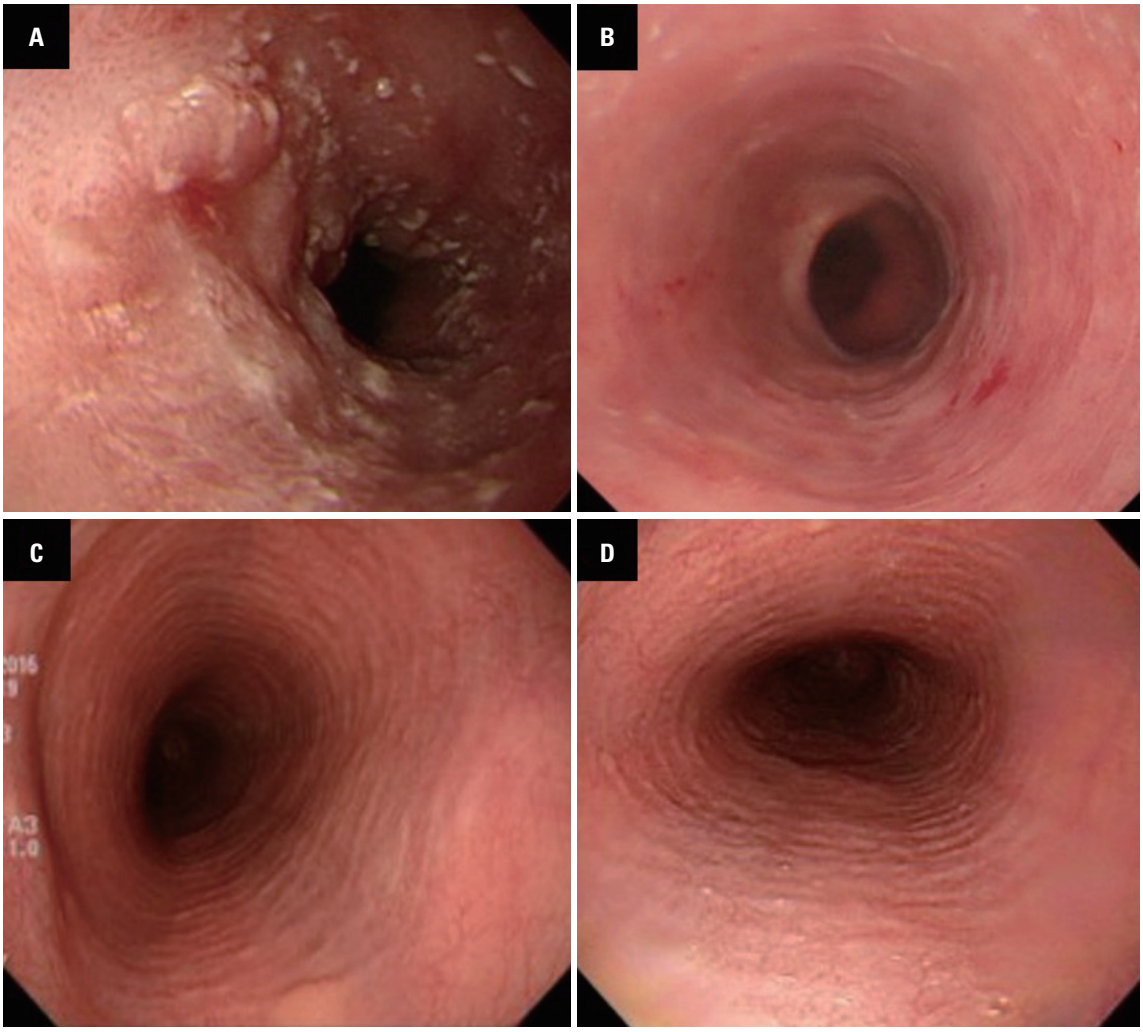

Fig. 3. Representative cases of irreversible endoscopic features. (A) Exudate, mucosal pale, and stricture of the esophagus were identified before treatment. (B) After balloon dilatation (13-mm balloon) and 8 weeks of treatment with a PPI, exudate and mucosal pale disappeared. Stricture had improved, but was still present. (C) Concentric rings were identified before treatment in a patient with eosinophilic esophagitis. (D) After 8 weeks of treatment with PPI, the patient's symptoms had resolved. However, the concentric rings remained. PPI, proton pump inhibitor.

of this disease are being explored, including clinical characteristics, underlying mechanisms, and effective treatment. The endoscopic features of EoE have been reported since early research on this disease.[16] However, they were not included in the initial diagnostic guidelines because the endoscopic features were inconsistent and poorly understood.[17,18] However, through various studies over the past 20 years, data on endoscopic features have accumulated.[12,19] Recently, efforts have been made to further systematize the endoscopic features of EoE, such as the EREFS system.[12]

In our study, we reviewed the endoscopy results of 33 patients before and after EoE treatment. We investigated their clinical characteristics, including endoscopic features and treatment outcomes. Male sex and middle age predominance were similar to those reported in previous studies.[20] The most common symptom was dysphagia, observed in about 50% of the EoE patients.[21] In this study, 48.4% of the patients had dysphagia. Seven asymptomatic patients were diagnosed with typical endoscopic features of EoE. These patients underwent endoscopy for gastric cancer screening and surveillance.

In a recent meta-analysis, longitudinal furrows, edema, and concentric rings were the most common endoscopic features in EoE patients.[22] In our study, edema was the most frequently observed finding, and the prevalences of other typical findings, such as furrows, exudate, and rings, were similar to those in previous studies. In previous studies, normal endoscopic findings have been reported in 4–20% EoE patients.[22-25] Patients with normal endoscopic findings were not included in this study. In the cohort of our study, some patients had normal endoscopic findings at the time of diagnosis, although they were excluded from this study because follow-up endoscopy was not performed after treatment. Rings and strictures are common endoscopic features in the fibrostenotic phenotype.[26] Patients with fibrostenotic changes are not expected to recover well, as ob-

served in our study. Although observed only in one patient, stricture persisted even after balloon dilatation and EoE treatment. After treatment, 82.7% of inflammatory features disappeared, whereas almost all fibro-stenotic features remained.

The limitations of our study are as follows: First, this was a retrospective study based on previous clinical and endoscopic images. We have reviewed all endoscopic images and results, but interobserver variations may occur in taking images or recording reports by several endoscopists over a long period of research. Second, the number of patients was small, as EoE is a rare disease. In addition, a number of patients refused follow-up endoscopy after their symptoms improved. Third, the interval time of follow-up endoscopy was not consistent. Despite these limitations, this is the first study to report on the reversibility of endoscopic features after treatment for EoE in South Korea.

In conclusion, we observed the reversibility of endoscopic inflammatory features of EoE. Fibrostenotic features were irreversible after esophageal remodeling in patients with EoE. These findings should be validated with further prospective, multi-center studies with long-term follow-up.

AUTHOR CONTRIBUTIONS

Conceptualization: Hyojin Park. Data curation: Hong Jin Yoon. Formal analysis: Hong Jin Yoon. Funding acquisition: Hyojin Park. Investigation: Hong Jin Yoon. Methodology: Hyojin Park and Hong Jin Yoon. Project administration: Hyojin Park. Resources: Hyojin Park. Software: Hong Jin Yoon. Supervision: Hyojin Park, Young Hoon Youn, and Jun Chul Park. Validation: Hong Jin Yoon. Visualization: Hong Jin Yoon. Writing—original draft: Hong Jin Yoon. Writing—review & editing: Hyojin Park, Young Hoon Youn, and Jun Chul Park. Approval of final manuscript: all authors.

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