

ORIGINAL ARTICLE

## 단일기관에서의 식도 호산구증가증에 대한 경험

조기원, 허철웅, 정다현, 윤영훈, 박효진

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### A Single-center Experience of Esophageal Eosinophilia

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**Background/Aims:** Esophageal eosinophilia occurs in many conditions, including eosinophilic esophagitis (EoE) and proton pump inhibitor-responsive esophageal eosinophilia (PPI-REE), which have been increasingly recognized in Western countries. There have been only a few reports in Korea. Here, we evaluated the clinical and endoscopic characteristics of patients with esophageal eosinophilia from our experience.

**Methods:** Nineteen patients were diagnosed with esophageal eosinophilia based on typical symptoms, endoscopic features, esophageal eosinophilia with  $\geq 15$  eosinophils/high power field, and response to medication by PPI. Symptoms, endoscopic and pathological findings were evaluated.

**Results:** Of the 19 patients, 2 patients were diagnosed with EoE, 7 patients were diagnosed with PPI-REE, and 10 patients were undetermined due to loss to follow-up. Among these 19 patients, dysphagia was present in 11, and heartburn, dyspepsia and reflux in 8. Sixteen patients had common endoscopic features, such as longitudinal furrows, concentric rings, strictures, and white plaques; however, 3 patients had normal findings. Nine patients underwent endoscopy at the time of follow-up. Two patients had complete resolution, and 3 had partial resolution. However, 4 patients showed no endoscopic changes. All patients showed symptom improvements.

**Conclusions:** The clinical and endoscopic characteristics of both groups in Korea were undistinguishable. However, after treatment, endoscopic findings were different between the two groups. Large-scale studies are warranted to confirm our findings. (**Korean J Gastroenterol 2018;72:10-14**)

**Key Words:** Esophagus; Eosinophilia; Proton pump inhibitors

### INTRODUCTION

Esophageal eosinophilia occurs in many conditions. It is primarily caused by chronic eosinophilic infiltration of esophageal epithelium. Eosinophilic esophagitis (EoE), proton pump inhibitor-responsive esophageal eosinophilia (PPI-REE), and gastroesophageal reflux disease are common diseases of

esophageal eosinophilia. EoE was first described in 1978, and PPI-REE was a newly acknowledged disease in 2006, which was distinct from EoE. PPI-REE is diagnosed when patients have typical esophageal symptoms and histologic features of esophageal eosinophilia, but show symptomatic and histologic response to a course of PPI therapy; since this time, the entity is considered distinct from EoE.<sup>1,2</sup> EoE is diagnosed

Received February 23, 2018. Revised April 19, 2018. Accepted April 25, 2018.

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Financial support: None. Conflict of interest: None.

in the absence of other causes of esophageal eosinophilia and unresponsiveness PPI therapy.<sup>3</sup>

In a previous Western study, PPI-REE was about one-third of esophageal eosinophilia.<sup>4</sup> Other studies demonstrated that a wide range 39-75% of adults with esophageal eosinophilia have PPI-REE.<sup>5,6</sup> Only a few studies regarding PPI-REE have been reported in Asian populations. A Japanese case series of 12 patients with esophageal eosinophilia reported that after PPI treatment, 2 patients (28.6%) were diagnosed with EoE, and 5 patients (71.4%) were diagnosed with PPI-REE.<sup>7</sup> In these studies, clinical, endoscopic, and histological features could not distinguish the two groups apart at baseline before PPI. These findings emphasize the necessity of a PPI trial as per the current guidelines to accurately diagnose EoE.

Dysphagia is the most common symptom with esophageal eosinophilia. Heartburn or dyspepsia has also been reported. Esophageal eosinophilia is more frequently observed in males, and the average age of onset is between the twenties and forties. Endoscopic features include longitudinal mucosal furrows, rings or circular corrugations, and long strictures in the body of the esophagus.<sup>8</sup>

Esophageal eosinophilia is an immune/antigen-mediated disease, in which food or environmental antigens stimulate an inflammatory response. It has frequently been associated with allergies, although the causal relationship has yet to be determined. Despite an increased understanding of inflammatory pathogenesis, changes of endoscopic findings, following the treatment of esophageal eosinophilia, has not been clearly defined to date. There has recently been an increase in the incidence and prevalence of esophageal eosinophilia due to the increasing recognition of EoE and PPI-REE;<sup>9,10</sup> however, there have been very few reports regarding these in Korea. Hence, we aimed to investigate the clinicopathologic characteristics of patients with EoE and PPI-REE from a single center's experience.

## SUBJECTS AND METHODS

We reviewed 19 patients with clinically, endoscopically, and histologically confirmed esophageal eosinophilia at a single university hospital between April 2007 and September 2016. Patients were diagnosed with EoE if they met the following criteria: (1) having symptoms related to esophageal

dysfunction; (2) mucosal eosinophilia in a esophageal biopsy with at least 15 eosinophils per high power field, which persisted even after a PPI therapeutic regimen; and (3) absence of other causes of esophageal eosinophilia. Patients were diagnosed with PPI-REE if they had esophageal symptoms and histologic features of esophageal eosinophilia, and a resolution of symptoms and histologic features after an 8-week course of a PPI therapeutic regimen.<sup>11</sup>

We checked the baseline characteristics, including sex, age, symptoms, and endoscopic findings. The typical symptoms that included dysphagia, heartburn, dyspepsia, and reflux were noted. We suspected esophageal eosinophilia when endoscopic findings showed longitudinal furrows, concentric rings, white plaque, and stricture. When esophageal eosinophilia was suspected, we obtained two to four biopsies to get sufficient specimens.

Treatment of esophageal eosinophilia consisted of PPI and or inhaled steroid (fluticasone propionate) for 8 weeks. After treatment, a follow-up endoscopy with esophageal biopsy and assessment of symptom change were performed.

This study was approved by the Institutional Review Board of Gangnam Severance Hospital, Yonsei University College of Medicine.

## RESULTS

Of the 19 patients (14 men and 5 women; mean age, 44.3 years) with esophageal eosinophilia, 10 did not undergo a follow-up endoscopy after treatment due to loss of follow-up. Two of 9 patients that underwent follow-up endoscopy were diagnosed with EoE and 7 patients were diagnosed with PPI-REE. The baseline characteristics, symptoms, and endoscopic findings are summarized in Table 1.

The mean age of patients with EoE was 44 years (range, 33 to 64), and 1 patient was male. Both EoE patients had symptoms with dysphagia, each patient had heartburn and reflux. One of 2 EoE patients had endoscopic findings with both of longitudinal furrows and concentric rings, but the other 1 patient had a normal endoscopic finding, even though he had typical esophageal symptoms. The mean age of patients with PPI-REE was 35 years (range, 19 to 56) and all 7 patients were males. Among the 7 PPI-REE patients, dysphagia was present in 4, heartburn in 2, and reflux in 1. Six of 7 PPI-REE patients had endoscopic findings with longitudinal furrows,

**Table 1.** Baseline Characteristics

	EOE	PPI-REE	Undetermined
N	2	7	10
Age, median (range)	44 (33-64)	35 (19-56)	50 (30-70)
Gender, male	1	7	6
Symptom			
Dysphagia	2	4	5
Heartburn	1	2	3
Dyspepsia	0	0	3
Reflux	1	1	1
Endoscopic findings			
Longitudinal furrows	1	6	6
Concentric rings	1	4	6
Stricture	0	1	0
White plaque	0	1	1
Normal finding	1	0	2

EOE, eosinophilic esophagitis; PPI-REE, proton pump inhibitor-responsive esophageal eosinophilia; N, Numbers.

4 had concentric rings, 1 had a stricture, and 1 had white plaques. All patients took a standard dose of PPI initially. Two EoE patients showed no symptom improvement within about 8 weeks after PPI medication. Hence, they were administered an inhaled corticosteroid. Seven PPI-REE patients showed symptom improvement within the 8-week period after PPI medication. Nine patients underwent endoscopy at the time of follow-up, but 10 patients were loss to follow-up. Two patients had complete resolution of endoscopic findings and 3 had partial resolution. However, 3 patients showed no endoscopic improvement and 1 patient, which had previous normal endoscopic finding, maintained normal endoscopic finding. Fig. 1 showed diverse alterations of endoscopic findings after treatment. Eight of 9 patients with EoE and PPI-REE showed histologic improvement, but 1 patient did not show any improvement. All patients with EoE and PPI-REE showed symptom improvement.

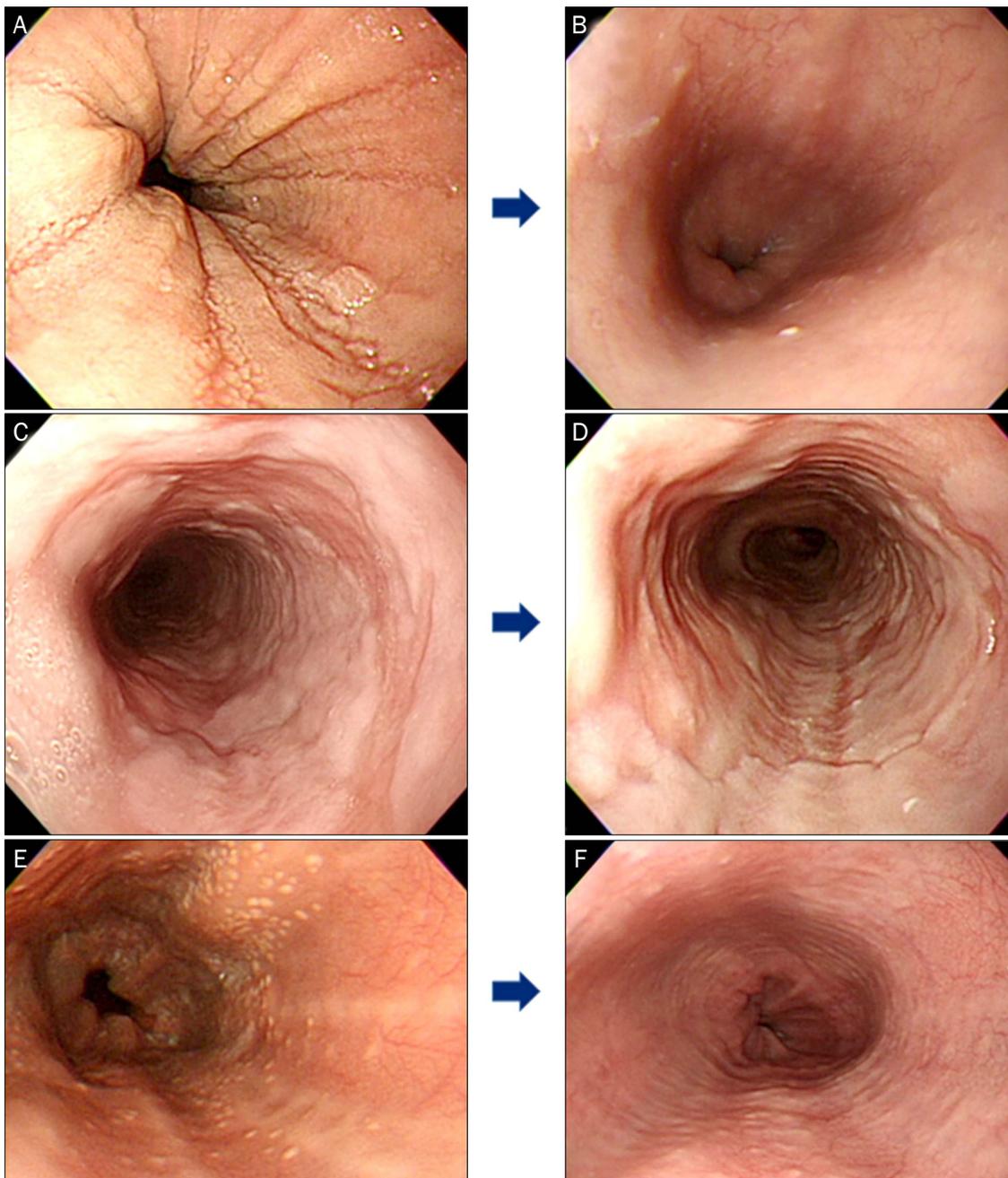
## DISCUSSION

Our understanding of esophageal eosinophilia with EoE have substantially advanced over the past 2 decades. However, acknowledgement of PPI-REE as a distinct entity from EoE has been a recent phenomenon. EoE and PPI-REE are now commonly encountered due to upper gastrointestinal symptoms and morbidity in both children and adults.<sup>3,12</sup>

In our study, we reviewed a total of 19 patients that included 9 patients with EoE or PPI-REE and 10 patients with

undetermined esophageal eosinophilia. Their clinicopathologic characteristics with the treatment outcomes were investigated and compared to previous studies.

The age and gender ratios in this study were similar to those in previous studies from both Western and Asian countries.<sup>13,14</sup> However, reasons for male preponderance of esophageal eosinophilia has yet to be clarified. Dysphagia, the most frequently reported symptom of esophageal eosinophilia in both Asian and Western countries, was found in about 50% of patients.<sup>14</sup> The main symptom was dysphagia, which was more than 50% of esophageal eosinophilia patients in this study. Heartburn, dyspepsia, and reflux were less common. In many previous studies, longitudinal furrows were most frequently observed endoscopic findings in both Asian and Western countries.<sup>15,16</sup> We reported that longitudinal furrows were most frequently observed and other typical findings, like concentric rings, stricture, and white plaque, were similar to previous studies. However, esophageal eosinophilia with normal endoscopic finding was higher in our study (15.8%) than in another study (8.8%).<sup>17</sup> This suggests that if esophageal eosinophilia is clinically suspected, histopathologic confirmation will be needed, despite normal endoscopic finding. In our study, clinicopathologic improvement or endoscopic alteration after treatment were comparable to those in other studies, but the ratio of PPI-REE to esophageal eosinophilia was higher in our study (77.8%) than in other studies.<sup>4-6</sup> The clinical and endoscopic findings was not distinguishable among those with PPI-REE, EoE, and undetermined esophageal eosinophilia, similar to other studies.<sup>14,17</sup>



**Fig. 1.** Treatment outcomes. (A) Initial endoscopic finding was linear furrow, which disappeared at the follow-up endoscopy (B) with improvement of eosinophilia. (C) Initial endoscopic finding was geographic shape furrow, which was maintained or aggravated at follow-up endoscopy (D) even if, eosinophilia disappeared. (E) Initial endoscopic finding was multiple white plaques with minimal concentric rings. (F) White plaques almost disappeared, but concentric rings remained. Eosinophilia disappeared.

We tried an 8 weeks trial of high-dose PPI initially when esophageal eosinophilia was confirmed to distinguish EoE and PPI-REE. In PPI-REE patients, there are several mechanisms attributed to symptomatic and histologic responses to PPI. First, some PPI-REE patients may have gastroesophageal reflux disease also, so a suppression of gastric acid by PPI may reduce symptoms. Moreover, PPIs have anti-inflammatory ef-

fects by reducing eosinophils by decreasing Th2 cytokine stimulated eotaxin-3 mRNA expression and protein secretion independent of the effects on acid production.<sup>11,17,18</sup> In our study, 7 of 9 patients that underwent follow-up endoscopy were improved after PPI trial. Their follow-up endoscopic changes were diverse, from complete or partial improvement to no endoscopic change, but all 7 patients with PPI-REE

showed histopathologic and symptomatic improvement. Two patients with EoE had normal finding of follow-up endoscopy after treatment with inhaled corticosteroid. They all had symptomatic improvement, but 1 of 2 patients showed no histopathologic improvement.

There are several limitations in this study. First, despite the long study period (10 years), only 19 patients were included. Furthermore 10 of 19 patients were lost to follow-up. Second, the interval time of follow-up endoscopy and treatment duration were not consistent. Third, in recently published papers from expert panels, PPI trial for diagnosis of PPI-REE from EoE was not recommended, because phenotypic, molecular, mechanistic, and therapeutic features cannot reliably distinguish PPI-REE from EoE. So they described that PPI trial brought more confusion than clarification, and suggested PPI-REE as a clinical sub-phenotype of EoE and not a distinct entity.<sup>1,19</sup> Therefore, in Korea, further, discussion of this controversy may be necessary, through a multicenter and prospective study with long term follow-up.

In conclusion, patients with EoE and PPI-REE in Korea were similar in clinicopathologic characteristics and endoscopic findings to those reported in other Asian and Western countries. However, the proportion of patients with normal endoscopic finding of esophageal eosinophilia and the ratio of PPI-REE to esophageal eosinophilia were higher in the Korean population compared with Western populations. Clinicopathologic response of treatment after PPI or steroid were satisfactory, but endoscopic improvement were various from patient to patient. This suggests that EoE and PPI-REE are chronic inflammatory diseases of the esophagus with irreversible change. Therefore, appropriate diagnosis and management will be necessary if esophageal eosinophilia is suspected.

## REFERENCES

- Molina-Infante J, Bredenoord AJ, Cheng E, et al. Proton pump inhibitor-responsive oesophageal eosinophilia: an entity challenging current diagnostic criteria for eosinophilic oesophagitis. *Gut* 2016;65:524-531.
- Landres RT, Kuster GG, Strum WB. Eosinophilic esophagitis in a patient with vigorous achalasia. *Gastroenterology* 1978;74:1298-1301.
- Dellon ES, Gonsalves N, Hirano I, et al. 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.
- Dellon ES, Speck O, Woodward K, et al. 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.
- Molina-Infante J, Ferrando-Lamana L, Ripoll C, et al. Esophageal eosinophilic infiltration responds to proton pump inhibition in most adults. *Clin Gastroenterol Hepatol* 2011;9:110-117.
- Sajej WN, Patel R, Baker RD, Tron E, Baker SS. Treatment with high-dose proton pump inhibitors helps distinguish eosinophilic esophagitis from noneosinophilic esophagitis. *J Pediatr Gastroenterol Nutr* 2009;49:393-399.
- Abe Y, Iijima K, Ohara S, et al. A Japanese case series of 12 patients with esophageal eosinophilia. *J Gastroenterol* 2011;46:25-30.
- Croese J, Fairley SK, Masson JW, et al. Clinical and endoscopic features of eosinophilic esophagitis in adults. *Gastrointest Endosc* 2003;58:516-522.
- Straumann A, Simon HU. Eosinophilic esophagitis: escalating epidemiology? *J Allergy Clin Immunol* 2005;115:418-419.
- Liacouras CA, Spergel JM, Ruchelli E, et al. Eosinophilic esophagitis: a 10-year experience in 381 children. *Clin Gastroenterol Hepatol* 2005;3:1198-1206.
- Park H. An overview of eosinophilic esophagitis. *Gut Liver* 2014; 8:590-597.
- Liacouras CA, Furuta GT, Hirano I, et al. Eosinophilic esophagitis: updated consensus recommendations for children and adults. *J Allergy Clin Immunol* 2011;128:3-20.e6; quiz 21-22.
- Furuta GT, Liacouras CA, Collins MH, et al. Eosinophilic esophagitis in children and adults: a systematic review and consensus recommendations for diagnosis and treatment. *Gastroenterology* 2007;133:1342-1363.
- Kinoshita Y, Ishimura N, Oshima N, Ishihara S. Systematic review: eosinophilic esophagitis in Asian countries. *World J Gastroenterol* 2015;21:8433-8440.
- Müller S, Pühl 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.
- 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.
- Jung DH, Yun GW, Lee YJ, Jo Y, Park H. Clinicopathologic analysis of proton pump inhibitor-responsive esophageal eosinophilia in Korean patients. *Gut Liver* 2016;10:37-41.
- Cheng E, Zhang X, Huo X, et al. Omeprazole blocks eotaxin-3 expression by oesophageal squamous cells from patients with eosinophilic oesophagitis and GORD. *Gut* 2013;62:824-832.
- Straumann A, Katzka DA. Diagnosis and treatment of eosinophilic esophagitis. *Gastroenterology* 2018;154:346-359.