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ORIGINAL ARTICLE

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양성자 펌프 억제제에 반응하는 식도 호산구증가증: 일개 대학병원 사례의 개요

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Proton Pump Inhibitor-responsive Esophageal Eosinophilia: An Overview of Cases from One University Hospital Center

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Background/Aims: Eosinophilic esophagitis (EoE) is a chronic, immune/antigen-mediated esophageal disease, with eosinophilic infiltration limited to the esophagus. A minority of EoE patients respond well to proton pump inhibitor (PPI) therapy alone, and that condition is labelled PPI-responsive esophageal eosinophilia (PPI-REE). The prevalence of PPI-REE among EoE cases is unknown. We aimed to identify clinical manifestations of PPI-REE, and the proportion of PPI-REE among all EoE cases. **Methods:** We reviewed pathology of the 4,075 patients who underwent esophageal biopsy at an institution from March 2003 to July 2015. EoE was diagnosed based on esophageal symptoms and eosinophilic infiltration limited to the esophagus, with ≥15 eosinophils per high-power field. We collected endoscopic and pathologic findings, and clinical features for these patients. **Results:** Thirteen (0.3%) patients were diagnosed with EoE. Clinical manifestations were dysphagia (30.8%), foreign body sensation (23.1%), regurgitation (23.1%), cough (15.4%), heartburn (15.4%), nausea (7.7%), dyspepsia (7.7%). The endoscopic findings noted were polypoid lesion (23.1%), whitish plaque or exudate (23.1%), linear furrow (7.7%), concentric ring (7.7%), nodularity (7.7%), erosion (7.7%), and normal (30.8%). Of these patients, five had a favorable course with PPI as monotherapy. **Conclusions:** The proportion of EoE among all patients undergoing endoscopic biopsy was 0.3%. Of those, PPI-REE comprised 38%. Most of the endoscopic findings were atypical or normal when compared to the typical findings in EoE. In conclusion, patients who present with symptoms related to esophageal dysfunction need esophageal biopsy, regardless of the endoscopic findings. Moreover, patients diagnosed with EoE need to be treated first with PPI alone. **(Korean J Gastroenterol 2016;67:178-182)**

Key Words: Eosinophilic esophagitis; Proton pump inhibitors; Eosinophilia; Eosinophils; Esophagus

INTRODUCTION

In the 1980s, esophageal eosinophilic infiltration was considered a pathognomonic finding in gastroesophageal reflux disease (GERD).[1,2] However, treatments for controlling acid exposure were not effective in some patients with this condition. Eosinophilic esophagitis (EoE) can be distinguished from GERD by clinicopathology.[3]

EoE is a chronic, immune/antigen-mediated disease with eosinophilic infiltration limited to the esophagus.[4,5] The first case of EoE was presented by Landres et al.[6] more than 40 years ago, and Attwood et al.[3] noted the first case of eosino-

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philic infiltration of the esophagus in adult patients.

In the United States, incidence of EoE increased from 0.35 to 9.45 per 100,000 persons per year from 1991-1995 to 2001-2005[7] and the prevalence of EoE was 56.7/100,000 persons in 2008-2011.[8] EoE diagnosis currently is gradually increasing in the United States.[7,8]

Several cases with eosinophilic infiltration of the esophagus reported a favorable effect with proton pump inhibitor (PPI) as monotherapy. These cases caused confusion about their classification as EoE or GERD.[9] Therefore, EoE with favorable response to PPI monotherapy is called PPI-responsive esophageal eosinophilia (PPI-REE).[10] PPI-REE is receiving increasing attention.[10-12]

There are few reports of prevalence of PPI-REE among EoE cases. We aimed to identify the proportion of PPI-REE among EoE cases and clinical manifestations of EoE at our hospital.

SUBJECTS AND METHODS

This retrospective study received institutional review board approval from Seoul National University Bundang Hospital (IRB No. B-1602-334-101), and informed patient consent was waived.

We reviewed the pathology of the 4,075 patients who underwent esophageal biopsy at Seoul National University Bundang Hospital from March 2003 to July 2015. EoE was diagnosed based on esophageal symptoms and eosinophilic infiltration with ≥15 eosinophils per high-power field (HPF). Exclusion criteria were (1) acute infection, (2) malignancy, (3) and no symptoms related to esophageal dysfunction or (4) eosinophilic infiltration on other segments of the gastrointestinal tract. Based on these criteria, we excluded 13 patients.

PPI-REE was diagnosed if patients presented with esophageal symptoms, histological features of esophageal infiltration with ≥15 eosinophils per HPF, and improvement of esophageal symptoms after PPI monotherapy alone. Baseline characteristics of patients with EoE were recorded, including age, sex, height, body weight, body mass index, social (smoking, alcohol) and past medical history. We also recorded symptoms, peripheral eosinophilic count, and endoscopic findings.

RESULTS

We diagnosed 26 patients with esophageal eosinophilia based upon ≥15 eosinophils per HPF. We excluded 13 patients who had acute infection, malignancy, or eosinophilic infiltration of other segments of the gastrointestinal tract and those who had no symptoms related to esophageal dysfunction. Among the excluded cases, one patient presented with an acute infection resembling actinomycosis, one patient with breast cancer, four patients with eosinophilic gastroenteritis, and seven patients with no symptoms related to esophageal dysfunction.

The proportion of patients who underwent random biopsy was 0.6% (24 patients) out of 4,075 patients. Four patients (16.7%) of those 24 patients were diagnosed with EoE.

After records search and exclusions, 13 (0.3%) patients with EoE were included in this study. The mean (±SD) age was

Table 1. Baseline Characteristics (n=13)

Characteristic	Data
Age (yr)	55.0±20.2
Gender, male	6 (46.2)
BMI (kg/m^2)	25.5±2.7
Smoking	3 (23.1)
Alcohol	4 (30.8)
Hypertension	5 (38.5)
Dyslipidemia	3 (23.1)
Diabetes mellitus	2 (15.4)
Asthma	2 (15.4)
Chronic eosinophilic pneumonia	1 (7.7)
Peripheral eosinophilia (≥500 eosinophils/mL)	4 (30.8)

Values are presented as mean±SD or n (%).

Table 2. Symptoms and Endoscopic Findings in Eosinophilic Esophagitis

Variable	Data
Symptom	
Dysphagia	4 (30.8)
Foreign body sensation	3 (23.1)
Regurgitation	3 (23.1)
Cough	2 (15.4)
Heartburn	2 (15.4)
Nausea	1 (7.7)
Dyspepsia	1 (7.7)
Endoscopic finding	
Polypoid lesion	3 (23.1)
Whitish plaque or exudate	3 (23.1)
Linear furrow	1 (7.7)
Concentric ring	1 (7.7)
Nodularity	1 (7.7)
Erosion	1 (7.7)
Normal	4 (30.8)

Values are presented as n (%).

55.0 (±20.2) years. There were six male patients (46.2%), the mean (±SD) body mass index was 25.5 (±2.7) kg/m^2, and four (30.8%) patients had peripheral eosinophilia. The baseline characteristics of the patients are summarized in Table 1.

The clinical manifestations were dysphagia (30.8%), foreign body sensation (23.1%), regurgitation (23.1%), cough (15.4%), heartburn (15.4%), nausea (7.7%), and dyspepsia (7.7%). Endoscopic findings were polypoid lesion (23.1%), whitish plaque or exudate (23.1%), linear furrow (7.7%), concentric ring (7.7%), nodularity (7.7%), erosion (7.7%), and normal aspect (30.8%) (Table 2).

Of the 13 patients, the symptoms of five (38.5%) diagnosed with EoE improved with PPI monotherapy. Five more (38.5%) patients' symptoms improved with a combination therapy (systemic glucocorticoid and/or topical steroid and/or leukotriene receptor antagonist). One (7.7%) patient did not improve with PPI as monotherapy, and two (15.4%) patients were diagnosed and then did not receive treatment.

Four EoE patients (30.8%) were treated with PPI before biopsy. Two of the five patients treated with PPI-REE were male. Patients with PPI-REE presented with a variety of clinical manifestations: foreign body sensation, dysphagia, regurgitation, heartburn, and dyspepsia. Endoscopic findings in patients with PPI-REE ranged from normal to erosion, nodular lesion with whitish exudate, polypoid lesion, and concentric ring as well. These patients presented with esophageal eosinophilic counts from 18 to more than 100 cells per HPF (Table 3, Fig. 1).

DISCUSSION

In our study, 0.3% of patients who underwent esophageal biopsies (13 patients) were diagnosed with EoE, and of those 13 cases, five were PPI-REE cases. This result was similar to other studies.[13-16] One study reported PPI-REE prevalence of 75% among cases with EoE.[17] Endoscopic findings alone cannot distinguish PPI-REE from EoE.[18,19] In our study, because of variable clinical manifestations and the preponderance of atypical endoscopic findings, we could not differentiate PPI-REE from EoE endoscopically.

Esophageal eosinophilia with a favorable course under monotherapy with PPI was first noted in 2006 by Ngo et al.[9] Three patients with esophageal eosinophilia and symptoms related to esophageal dysfunction had histologic and symptomatic responses to PPI monotherapy.[9] EoE is an immune-mediated condition, wherein food or environmental antigens trigger a type 2 T-helper mediated response in genetically predisposed individuals via cytokines. These medi-

Table 3. Symptoms and Endoscopic Findings and Eosinophilic Infiltrative Count in PPI-REE

Case	Sex/age (yr)	Symptoms	Endoscopic finding	Eosinophil count/HFP
1	M/55	Foreign body sensation	Normal	18
2	F/72	Dysphagia	Erosion on GEJ	30
3	M/80	Regurgitation	Nodular lesion with whitish exudate on mid to distal esophagus	35
4	F/58	Heartburn	1 cm sized polypoid lesion on GEJ	>100
5	F/34	Dyspepsia	Concentric rings on lower esophagus	>100

PPI-REE, proton pump inhibitor-responsive esophageal eosinophilia; HFP, high-power field; M, male; F, female; GEJ, gastroesophageal junction.

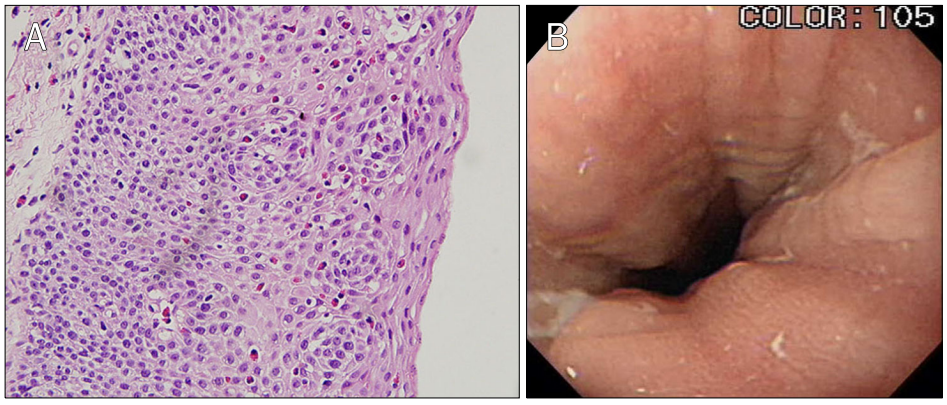

Fig. 1. Initial histologic finding (H&E, ×400) and endoscopic finding in No. 5 patient with proton pump inhibitor-responsive esophageal eosinophilia. (A) Biopsy of the esophageal mucosa showed infiltration of eosinophils (>100 eosinophils/high-power field). (B) Concentric rings in lower esophagus.

ators stimulate esophageal production of eotaxin-3 and recruitment and activation of eosinophils in the esophageal mucosa.[20] Esophageal eotaxin-3 is an important element for promoting eosinophil chemotaxis.[21] Recent studies show that the pathogenesis of PPI-REE and EoE is similar.[22,23]

However, in PPI-REE, symptoms and histological features improve with PPI therapy, similar to GERD.[15,17,18] Furthermore, esophageal eosinophilia is seen in patients with GERD.[19,22] Therefore, it is difficult to differentiate PPI-REE from EoE and GERD, by clinical or histologic findings before PPI therapy.[22] This may cause confusion in diagnosis and treatment of these medical entities.

PPI treatment response in patients with PPI-REE are attributed to several mechanisms. One hypothesis is that the PPI response in PPI-REE is through an acid-suppression mechanism, treating combined GERD.[24] Acid exposure could cause esophageal epithelial damage followed by penetration of allergic antigens that trigger an eosinophilic infiltration in the mucosa.[25] Another potential mechanism is based on the anti-inflammatory effect of PPI. PPI has an anti-oxidant effect and a direct influence on cells that could prevent inflammation, such as neutrophils, monocytes, endothelial and epithelial cells.[26]

According to current guidelines, if eosinophilia is confined to the esophagus, then EoE, GERD, and PPI-REE are the clinical possibilities. In such a situation, a PPI trial for two months, followed by repeat endoscopy and biopsy, is recommended. On repeat biopsy, if eosinophilia persists and symptoms are still present, then EoE can be diagnosed. If the clinical course is favorable and symptoms and eosinophilia improve, then PPI-REE is the most likely diagnosis. Some patients diagnosed with PPI-REE have GERD with esophageal eosinophilia.[4]

This study has some limitations. First, because it was a retrospective study, patients were not treated according to the same PPI protocol. Another drawback of the retrospective study design is the lack of histological confirmation of PPI response. Therefore, we diagnosed PPI-REE only by clinical symptoms. Finally, some patients were treated first with a combination therapy (glucocorticoid and/or leukotriene receptor antagonist and/or topical steroid).

Currently, data on patients with PPI-REE are lacking. Future large prospective design studies are required in order to better diagnose and treat patients with PPI-REE.

In conclusion, of patients who underwent esophageal biopsies, 13 (0.3%) were diagnosed with EoE, and of those 13 cases, five were PPI-REE cases. Among endoscopic findings, we encountered more atypical or normal findings in EoE than typical findings. Therefore, patients who have symptoms related to esophageal dysfunction need esophageal biopsy, regardless of the endoscopic findings. Patients diagnosed with EoE should receive an initial trial of PPI alone.

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