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 ≥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 indistinguishable. 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.\textsuperscript{1,2} EoE is diagnosed...
in the absence of other causes of esophageal eosinophilia and unresponsiveness PPI therapy.3

In a previous Western study, PPI-REE was about one-third of esophageal eosinophilia.4 Other studies demonstrated that a wide range 39-75% of adults with esophageal eosinophilia have PPI-REE.5,6 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.7 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.8

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;9,10 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.

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 were 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

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

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. 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.3,12

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.13,14 However, reasons for male preponderance of esophageal eosinophilia has yet to be clarified. Dysphagia, the most frequently reported symptom 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.14 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.15,16 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%).17 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.4,6 The clinical and endoscopic findings was not distinguishable among those with PPI-REE, EoE, and undetermined esophageal eosinophilia, similar to other studies.14,17
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 effects by reducing eosinophils by decreasing Th2 cytokine stimulated eotaxin-3 mRNA expression and protein secretion independent of the effects on acid production. 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. 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