学 位 論 文 の 要 旨

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学 位 論 文 名　Similarities and Differences Among Eosinophilic Esophagitis, Proton-Pump Inhibitor-Responsive Esophageal Eosinophilia, and Reflux Esophagitis: Comparisons of Clinical, Endoscopic, and Histopathological Findings in Japanese Patients

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論 文 内 容 の 要 旨

INTRODUCTION

Eosinophilic esophagitis (EoE) is characterized by chronic inflammation with dense eosinophile infiltration in the esophageal epithelial layer as well as esophageal symptoms including dysphagia and heartburn, and is thought to be based on an allergic and immunological pathogenesis. Because the presence of esophageal eosinophilia is not specific for EoE, consensus guidelines require clinical and/or histologic unresponsiveness to acid-suppressive therapy by proton pump inhibitor (PPI) to exclude other causes of esophageal eosinophilia, such as gastroesophageal reflux disease (GERD). Recently, it has become apparent that some patients with a phenotype appearance of EoE and distinct from GERD respond histologically to PPI. These patients are described as having PPI-responsive esophageal eosinophilia (PPI-REE), to distinguish them from EoE patients. However, the underlying pathogenic mechanism of PPI-REE is poorly understood and several studies have called into question how to make a proper distinction between EoE and PPI-REE.

In the present study, clinical, endoscopic, and histopathological findings in cases of EoE, PPI-REE, and reflux esophagitis (RE) in Japan were analyzed and compared in order to find

possible predictive factors for PPI responsiveness in Japanese patients.

MATERIALS AND METHODS

Eleven patients diagnosed with EoE, 16 with PPI-REE, and 39 with RE, who were all consecutively examined from 2005 to 2015 at Shimane University Hospital, were enrolled in this retrospective study. Clinical data including demographics (age, gender, height, weight), clinical presentation (dysphagia, heartburn, etc.), atopic background (bronchial asthma, atopic dermatitis, etc.), and peripheral blood test results were independently extracted from the medical records of the enrolled patients. Images obtained with endoscopy were reviewed and classified according to a standardized method. Mucosal breaks in patients with RE were graded according to the Los Angeles classification. Typical endoscopically identifiable mucosal lesions of EoE/PPI-REE, such as the presence of esophageal longitudinal furrows, multiple concentric rings, strictures, and white plaque, were evaluated. Histopathological findings of biopsy samples were reviewed by surgical pathologists. The maximal numbers of eosinophils, lymphocytes, and neutrophils per high power field were determined. In addition, the presence of epithelial basal cell hyperplasia, balloon cells, and dilated intercellular spaces in the middle epithelial layer (spongiosis) was evaluated. Statistical comparisons between groups were made by ANOVA, followed by a Mann–Whitney U test. A chi-squared test was also used as appropriate. $P < 0.05$ was considered to indicate a statistically significant difference. The study protocol was approved by the Ethics Committee of Shimane University.

RESULTS AND DISCUSSION

The differences in the clinical characteristics of EoE and PPI-REE were not remarkable, though patients with EoE and PPI-REE were younger, had greater numbers of allergic comorbidities, and complained of symptoms of dysphagia more frequently than those with RE. The only noteworthy differences between EoE and PPI-REE were more frequent reports of

asthma (36.4 vs. 12.5 %) and food allergy (27.3 vs. 0 %) by patients with EoE ($P < 0.05$, $P < 0.05$, respectively). Thus, PPI-REE was considered to be ranked between RE and EoE in terms of frequency of accompanying allergic diseases. Consistently, plasma total IgE concentration was significantly higher in the EoE group as compared to the PPI-REE group.

As for endoscopic findings, esophageal mucosal longitudinal furrows, multiple concentric rings, and white plaque were more frequent in the EoE and PPI-REE groups as compared to RE. Notably, there was a significantly increased prevalence of longitudinal furrows and white plaque in the EoE and PPI-REE groups, and these findings were considered to be specific for diagnosis in those patients. However, there was no significant difference between EoE and PPI-REE in regard to endoscopic findings.

Dense eosinophile infiltration was found in the EoE and PPI-REE groups, and the number of eosinophils was also similar in both groups. On the other hand, only a small number of infiltrating eosinophils was found in the RE patients. There is no histopathological differences between EoE and PPI-REE.

From our observations, we speculate that an allergic condition, such as a high count of peripheral eosinophils, a high level plasma IgE level, and an atopic background, indicates a poor response to PPIs in patients with esophageal eosinophilia. However, the difference between the EoE and PPI-REE cases were marginal, and there were no independent clinical, endoscopic, or histological predictors that reliably distinguished PPI-REE from EoE in multivariate analysis.

CONCLUSION

Comparisons of clinical, endoscopic, and histopathological findings of patients with EoE, PPI-REE, and RE revealed nearly no difference in esophageal mucosal histopathological findings between those with EoE and PPI-REE. On the other hand, our data suggested that patients with EoE are more prone to comorbid allergic disease. Predicting PPI responsiveness in cases with esophageal eosinophilia is difficult and requires further investigation.