

## 学位論文の要旨

氏名 焦 遯 進

- 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.

論文審査及び最終試験又は学力確認の結果の要旨

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論文審査の結果の要旨

好酸球性食道炎 (EoE) は食道粘膜上皮への好酸球浸潤を病理学的特徴とする慢性アレルギー疾患であり、近年、本邦においても報告例が増加している。欧米のガイドラインでは食道好酸球浸潤例のうち、酸分泌抑制薬であるプロトンポンプ阻害薬 (PPI) の無効例を EoE と定義しており、PPI 有効例は、PPI 反応性食道好酸球浸潤 (PPI-REE) として区別されるが、2つの病態の相違について日本人を対象とした検討はない。申請者らは、EoE、PPI-REE、および逆流性食道炎の臨床的特徴の相違点を明らかにすることを目的として本検討を行った。

2005年から2015年の間に島根大学医学部附属病院で診断されたEoE11例、PPI-REE16例を対象とした。また、鑑別疾患として重要である逆流性食道炎症例39例を対照群とした。診療録から、症状、アレルギー疾患の合併、血液検査所見、内視鏡所見、組織学的所見のデータを抽出し、各群間で比較検討した。年齢・男女比、臨床症状についてEoE群とPPI-REE群で差は認められなかったが、アレルギー疾患の合併については、EoE群で他群に比して、喘息および食事アレルギーの合併率が有意に高かった。また、血清IgE値もEoE群で有意に高値であった。内視鏡所見、組織学的所見についてはEoE群とPPI-REE群で有意な差は認められなかった。これらの結果から、EoE群とPPI-REE群の臨床的特徴では顕著な相違はないものの、EoE群でアレルギーの関与が強い傾向があることが明らかとなった。本研究は、日本人における食道好酸球浸潤の臨床像について新たな知見を示したものであり、臨床的に有用な成果と考えられる。

最終試験又は学力の確認の結果の要旨

申請者は、内視鏡および組織学的所見を中心に多くの要素について EoE, PPI-REE の違いを検討し、いくつかの相違点はあるものの、両病態の間に本質的な差が認められないことを示した。公開審査においては、質疑に対して真摯な態度で適切な対応が出来ており、背景の知識も充分であることから、学位に値すると判断した。  
(主査：並河 徹)

本論文は、好酸球性食道炎の疫学、病態、診断、治療について、罹患率の少ない症例を数多く集積した上で、詳細な検討を加えた独自性のある臨床研究である。本学の学位に値する内容であると判断する。  
(副査：川内秀之)

申請者は、好酸球性食道炎、プロトンポンプ阻害薬反応性食道好酸球浸潤及び逆流性食道炎における臨床的、内視鏡的及び病理組織学的異同について明らかにした。関連領域の学識、考察力も充分あり、学位授与に値すると判断した。  
(副査：熊倉俊一)

(備考) 要旨は、それぞれ 400 字程度とする。