学 位 論 文 の 要 旨

氏名　沖本　英子

学 位 論 文 名　Specific Locations of Linear Furrows in Patients With Esophageal Eosinophilia.

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著 者 名　Eiko Okimoto, Norihisa Ishimura, Mayumi Okada, Daisuke Izumi, Hironobu Mikami, Masahito Aimi, Takashi Tanimura, Tsuyoshi Mishiro, Naoki Oshima, Noriyoshi Ishikawa, Shunji Ishihara, Kyoichi Adachi, Riruke Maruyama, Yoshikazu Kinoshita.

論 文 内 容 の 要 旨

INTRODUCTION

Eosinophilic esophagitis (EoE) is a clinicopathological condition characterized by symptoms of esophageal dysfunction, typical endoscopic findings, and dense esophageal eosinophilia (EE), which is defined as more than 15 eosinophils per high-power field (HPF) in at least one esophageal biopsy specimen. The clinical features of EoE are non-specific and can overlap those of gastroesophageal reflux disease (GERD), making it difficult to distinguish between those conditions in clinical settings. In addition, gastroesophageal reflux may play an important role in the development of EE, as gastric acid suppression by giving proton pump inhibitor is effective in more than half of patients with EE.

Recent study shows that over 90% of patients with EE have abnormal endoscopic findings, such as linear furrows, which is the most common findings. However, the precise endoscopic features remain to be fully elucidated. In the present study, we sought to clarify the endoscopic features of EE, essential for the diagnosis of EoE, by focusing on the specific locations of linear furrows in a Japanese population.

MATERIALS AND METHODS

We retrospectively enrolled 70 patients with EE who were diagnosed at Shimane University Hospital between July 2005 and January 2016. Information regarding endoscopic findings and clinical parameters was obtained and reviewed. To clarify the endoscopic features of EE, we focused on the specific locations of linear furrows. In cases with linear furrows, their specific locations, including circumferential location, longitudinal distribution, and position in relation to esophageal longitudinal folds (ridge or valley), were noted. As a control group, another 108 consecutive patients with reflux esophagitis (RE), Los Angeles grade A or B, who were endoscopically diagnosed at our hospital between January and May 2015 were also enrolled. Position of mucosal breaks in relation to esophageal longitudinal folds was also evaluated in the same manner as linear furrows in the EE patients. Finally, the relationship between linear furrows and eosinophilic infiltration was evaluated. Biopsy specimens were obtained from linear furrows in valleys as well as mucosa on adjacent ridges between valleys, and peak eosinophil count/HPF was compared between those locations. The study protocol was approved by the Ethics Committee of Shimane University.

RESULTS AND DISCUSSION

The 70 enrolled patients consisted of 57 males and 13 females, with a mean age of 48.1 ± 14.4 years (range 17-85 years). EE was frequently observed in middle-aged patients with a peak age of occurrence in the 40s and 71% had concurrent allergic diseases. As for endoscopic findings, linear furrows, whitish exudates, and rings were frequently observed, and at least one of those findings was seen in every cases. Of these, linear furrows (n=63) were the most frequently found endoscopic abnormality in patients with EE.

Linear furrows were found to be longitudinally widespread throughout the lower to middle or upper esophagus in 51 (81%), whereas these were localized in the lower esophagus in 12

(19%). As for circumferential location, linear furrows were seen in all circumferential directions in a radial pattern in each of these patients. In addition, all of the linear furrows were found in esophageal longitudinal mucosal fold valleys, whereas none appeared on ridges. Our findings indicate that particular attention should be paid to mucosa in longitudinal fold valleys for detection of linear furrows, especially in the lower esophagus.

In contrast, the vast majority (93%) of mucosal breaks in RE cases were located on mucosal fold ridges and mainly found on the right anterior wall of the esophagus. These findings were consistent with those of our previous studies, and showed that localization of mucosal breaks was apparently different from that of linear furrows in EE patients, suggesting that acid reflux is not directly associated with formation of linear furrows in those patients.

Finally, we obtained biopsy specimens from 15 patients with linear furrows to determine the relationship between linear furrows and eosinophilic infiltration. Increased eosinophilic infiltration was significantly more frequent in linear furrows in the valleys (93%) as compared to mucosa on adjacent ridges (60%) ($P < 0.05$), indicating that fewer biopsies from linear furrows should be sufficient for an accurate diagnosis.

CONCLUSION

Our analysis included the largest number of EE cases reported in Japan. All had abnormal endoscopic findings, such as linear furrows, which was the most common. Linear furrows were detected in a radial pattern and were widespread throughout the lower to middle or upper esophagus. Furthermore, they were found only in the longitudinal mucosal fold valleys but not on the ridges, which is a completely different location as compared to mucosal breaks in RE cases. Eosinophilic infiltration $\geq$ 15/HPF was also more frequently found in linear furrows located in the valleys as compared to mucosa on adjacent ridges. More detailed investigation of these characteristics, especially by focusing on linear furrows in esophageal mucosal fold valleys, may provide important clues for more accurate diagnosis of EoE.

論文審査及び最終試験又は学力の確認の結果の要旨

(甲)・乙	氏名	沖本　英子
学位論文名	Specific Locations of Linear Furrows in Patients With Esophageal Eosinophilia	
学位論文審査委員	主査	森田栄伸　印
	副査	原田　守　印
	副査	関根浄治　印

論文審査の結果の要旨

近年、本邦で増加傾向にある好酸球性食道炎の診断には病理学的に食道好酸球浸潤を証明することが必須であるが、内視鏡像の特徴や食道内の好酸球浸潤の分布などは十分には明らかでない。申請者らは、好酸球性食道炎の内視鏡所見を詳細に検討するとともに、最も高頻度に認められる縦走溝という所見に注目し、内視鏡所見と好酸球浸潤との関連、治療効果による変化を明らかにすることを目的として本検討を行った。

島根大学医学部附属病院で食道好酸球浸潤と診断され、内視鏡所見の評価が可能であった70例を対象とした。また、縦走溝と鑑別が必要な縦走する粘膜傷害をきたす逆流性食道炎症例108例を対照群とした。縦走溝は70例中、63例（90%）に認められた。縦走溝は食道の下部から上部まで広範囲に放射状に存在し、縦走する襞の間の谷の部分に認められた。この特徴は逆流性食道炎で認められる粘膜傷害とは全く異なるものであった。縦走溝と隣接する峰の部分から生検を行い、浸潤好酸球数を比較したところ、高倍率視野あたり15個以上の好酸球浸潤を認めた症例は有意に縦走溝の部分で多かった。さらに、プロトンポンプ阻害薬（PPI）投与後の内視鏡像の評価を行い、PPIに反応する症例では全例で縦走溝が消失したが、PPIに反応しない症例では半数以上で縦走溝の残存を認めた。これらの結果は、好酸球性食道炎の診断や治療効果の判定における新たな知見を示したものであり、臨床的に意義の高い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、好酸球性食道炎の内視鏡所見と病理組織所見を臨床的に検討し、縦走溝が特異度の高い所見で、縦走溝の部位に好酸球浸潤が強く見られること、PPIによる治療反応群では縦走溝が消失することを見出した。これらの結果は好酸球性食道炎の診療に有用な知見であり、また質疑にも極めて的確に応答したことから、学位授与に値すると判断した。（主査：森田栄伸）

申請者は、好酸球性食道炎の内視鏡所見と生検の病理所見を検討することにより、好酸球性食道炎患者での好酸球浸潤の分布の特徴を明らかにした。研究成果は、好酸球性食道炎の診断や治療に役立つものである。関連知識も十分で、学位授与に値すると判断した。（副査：原田　守）

本研究は、食道好酸球増加症の内視鏡的診断基準を確立する目的で企画された。申請者は、食道好酸球浸潤に特徴的な形態すなわち縦走溝に着目し、生検標本と比較検討を行い、縦走溝の存在が食道好酸球増加症の内視鏡診断に極めて有用であることを明らかにした点で臨床的に意義深い。関連知識もあり、学位授与に相応しいと判断した。（副査：関根浄治）

（備考）要旨は、それぞれ４００字程度とする。