Original article

Specific locations of linear furrows in patients with esophageal eosinophilia

Running title: Furrows in esophageal eosinophilia

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Abstract

Objectives: Several characteristic endoscopic findings, such as linear furrows, rings, and whitish exudates, indicate the presence of eosinophilic esophagitis (EoE). Although linear furrows are the most frequently found endoscopic abnormality in affected patients, the precise endoscopic features remain to be fully elucidated. Here, we aimed to clarify the endoscopic features of esophageal eosinophilia (EE), essential for diagnosis of EoE, by focusing on the specific locations of linear furrows in a Japanese population.

Methods: We enrolled 70 cases with EE (≥15 eosinophils/high power field) who were diagnosed at our hospital and related facilities. Information regarding endoscopic findings and clinical parameters was retrospectively reviewed. Next, the position of linear furrows in relation to esophageal longitudinal folds (ridge or valley) was evaluated in each case and compared with the position of mucosal breaks in patients with reflux esophagitis. Finally, the relationship between linear furrows and eosinophilic infiltration was evaluated.

Results: Of the 70 EE patients, 63 (90%) had linear furrows. Those occurred in a radial pattern and were widespread throughout the lower to upper esophagus, and exclusively found in esophageal longitudinal mucosal fold valleys, not on ridges, which was different from the position of mucosal breaks in patients with reflux esophagitis. Increased eosinophilic infiltration was significantly more frequent in linear furrows in the valleys (93%) as compared to mucosa on adjacent ridges (60%) ($P<0.05$).

Conclusions: Investigation of these endoscopic characteristics, especially by focusing on linear furrows in esophageal mucosal fold valleys, may provide

important clues for more accurate diagnosis of EoE. UMIN000018704.

Keywords: eosinophilic esophagitis, eosinophilia, reflux esophagitis, endoscopy

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.[1,2] Over the past two decades, the prevalence of EoE has been rapidly increasing in Western countries.[3-5] Although affected patients are also increasingly being reported in Asia, the disease is thought to be rare in Asian populations.[6,7]

The clinical features of EoE are nonspecific and can overlap those of gastroesophageal reflux disease (GERD), making it difficult to distinguish between those conditions in clinical settings.[8,9] Endoscopic findings of EoE include linear furrows, rings, whitish exudates, strictures, edema, and pallor or decreased vasculature.[10,11] Although previous studies reported that approximately 30% to 40% of patients with EoE had no characteristic endoscopic findings,[12,13] more recent prospective studies conducted not only in Western countries, but also Asian countries, have found that at least one abnormality was detected by endoscopy in over 90% of EoE patients.[6,7,11] Among those findings, linear furrows are one of the most characteristic and specific findings in affected patients, with high inter-observer agreement.[14] In addition, we recently showed that linear furrows were the most frequent finding and useful for diagnosis of EE.[15] However, most studies conducted in Japan have been reported as case series and assessed only a small number of patients (10-26 cases), and the detailed endoscopic features of linear furrows remain to be fully elucidated.[16,17]

In the present study, we aimed to clarify the endoscopic features of EE, essential for diagnosis of EoE, by focusing on specific locations of linear furrows in a Japanese population. We analyzed 70 cases of EE, the largest number of such cases reported in a single study in Japan, and also examined the cause of linear furrows as compared to positions of mucosal breaks in patients with reflux esophagitis (RE).

METHODS

Enrolled subjects and data collection

We retrospectively enrolled 70 patients with EE who were diagnosed at Shimane University Hospital and related facilities between July 2005 and January 2016. Histological diagnosis of EE was defined as the presence of ≥15 eosinophils per HPF in biopsy samples obtained with endoscopy. Patients with a systemic cause of EE, including eosinophilic gastroenteritis, Crohn's disease, parasites, drug hypersensitivity, and hypereosinophilic syndrome, were excluded. Information regarding endoscopic findings and clinical parameters, including symptoms, allergy comorbid rate, laboratory findings, and response to proton pump inhibitor (PPI) administration, was obtained and reviewed.

EoE was defined clinically by symptoms of esophageal dysfunction and histologically by the presence of EE, as well as lack of response to a course of PPI treatment administered according to current guidelines.[1,2] Furthermore, PPI-responsive esophageal eosinophilia (PPI-REE) was defined as presentation of clinical symptoms similar to those of EoE, with both symptoms and eosinophilic infiltration disappearing by PPI treatment at a standard or double dose within 2

months of beginning administration.

The protocol of this study was evaluated and approved by the Ethical Committee of Shimane University School of Medicine and related facilities. This study was registered with the University Hospital Medical Information Network (UMIN) clinical trials registry (UMIN 000018704).

Assessment of endoscopic findings

To clarify the endoscopic features of EE, we focused on the specific locations of linear furrows. Images obtained with endoscopy were separately reviewed by three of the authors (E.O., N.I., N.O.) to determine the presence and location of linear furrows in each case. Linear furrows were defined as longitudinal grooves or crevices parallel to the length of the esophagus,[11] which can be clearly detected by white light endoscopy. The examiners were blinded in regard to the clinical diagnosis of each case and the endoscopic diagnosis was established by consensus of at least two of the three. 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 RE, Los Angeles grade A or B,[18] who were endoscopically diagnosed at Shimane University Hospital between January and May 2015 were also enrolled. The position of mucosal breaks in relation to esophageal longitudinal folds was also evaluated in the same manner as linear furrows in the EE patients. The circumferential locations of mucosal breaks on the esophageal wall were evaluated as on a clock

face, as follows. With anterior wall of the esophagus always positioned at 12 o'clock, the 3 o'clock position was defined as the right lateral wall of the esophagus aligned with the lesser curvature of the stomach. The presence or absence of a hiatal hernia,[19] as well as gastric mucosal atrophy[20] were also investigated in each case using endoscopic findings.

Relationship between linear furrows and eosinophilic infiltration

EoE is a patchy disease in which eosinophil infiltrates are known to appear in various locations throughout the entire esophagus.[21] Endoscopic appearances, such as linear furrows and whitish exudates, may be associated with high eosinophil density. Therefore, we sought to determine the relationship between linear furrows and eosinophilic infiltration. We obtained biopsy specimens from 15 of the EE patients with linear furrows. In those patients, at least one biopsy specimen was obtained not only from linear furrows in valleys, but also mucosa on adjacent ridges. Peak eosinophil count/HPF were compared between those locations.

Statistical analysis

Statistical analyses were carried out using chi-squared and Mann–Whitney U-tests. Wilcoxon's signed rank test was used for a comparison of peak eosinophil count/HPF between linear furrows in the valleys and adjacent ridges. P values <0.05 were considered to indicate statistical significance. All statistical analyses were performed using the SPSS statistical analysis software package (version 22.0 for the PC, Chicago, IL, USA).

RESULTS

Basic clinical characteristics of enrolled patients

The demographic and clinical characteristics of the patients are shown in **Table 1**. The 70 enrolled patients consisted of 57 males and 13 females, with a mean (± SD) age of 48.1±14.4 years (range 17-85 years). Consistent with previous reports, the male/female ratio was approximately 4 to 1, with typical male predominance. EE was frequently observed in middle-aged patients with a peak age of occurrence in the 40s and 71% had concurrent allergic diseases.

Sixty-one of our 70 patients with EE were symptomatic, with dysphagia the most common symptom observed, followed by heartburn and epigastralgia. None had a history of food impaction, in contrast to Western EoE patients in whom that frequently occurs.[22]

As for endoscopic findings, linear furrows, whitish exudates, and rings were frequently observed, and at least 1 of those findings was seen in every case. Of them, linear furrows was the most frequently found endoscopic abnormality in patients with EE.

Specific locations of linear furrows

Of the 70 patients with EE, 7 were excluded from further evaluation because of a lack of linear furrows in endoscopic findings. Those 63 cases consisted of 53 males and 10 females, with a mean age of 47.3±13.4 years (range 17-85 years). Linear furrows were found to be located in a longitudinally widespread throughout the lower to middle or upper esophagus in 51 (81%), while those were

localized in the lower esophagus in 12 (19%). Interestingly, linear furrows in all cases were detected in the lower esophagus, but not in localized at the upper or middle esophagus. As for circumferential location, linear furrows were seen in all circumferential directions in a radial pattern in each of these patients (**Figure 1A, B**). The position of linear furrows in relation to esophageal longitudinal folds was also assessed. Under physiological conditions, the mucosa and submucosa form longitudinal folds in the empty esophagus. Therefore, it is of great interest to determine whether linear furrows are formed in mucosal fold valleys or on the ridges between valleys. Importantly, all of the linear furrows observed in our patients were found in esophageal longitudinal mucosal fold valleys, while none appeared on ridges (**Figure 1C, D**) (**Video 1**).

Specific locations of mucosal breaks

Acid suppression by PPI administration is known to be effective for more than half of patients diagnosed with EE, thus we speculated that gastroesophageal acid reflux plays an important role in the formation of linear furrows in those patients. In the present study, the position of mucosal breaks in RE was also examined. We enrolled 108 RE patients with Los Angeles grade A or B, who consisted of 78 males and 30 females, with a mean age of 66.3±12.4 years (range 34-103). The patients with RE were significantly older than the cohort with EE ($P<0.0001$). Most of the mucosal breaks in these patients (87%) were found to be localized in the lower esophagus. In addition, those were mainly located on the right anterior wall (from 12 o'clock to 3 o'clock) of the esophagus and predominantly on mucosal fold ridges (93%) (**Figure 2**) (**Video 2**). These findings

were consistent with those of our previous studies,[23,24] and showed that localization of mucosal breaks was apparently different from that of linear furrows in EE patients.

Relationship between linear furrows and eosinophilic infiltration

We obtained biopsy specimens from 15 patients with linear furrows (13 males, 2 females; mean age 48.6±13.3 years, range 30-76 years). At least 1 specimen was obtained from those located in valleys and 1 from an adjacent ridge between valleys (**Figure 3A**). The median value for peak eosinophil count/HPF showed no significant difference between the valley and ridge specimens (30 vs. 20, P=0.11). To accurately diagnose EE, esophageal eosinophilic infiltration ≥15/HPF must be confirmed with histological results. Thus, we assessed the positive rate for eosinophilic infiltration ≥15/HPF in each group and found that it more frequently occurred in linear furrows located in the valleys (93%) as compared to those on adjacent ridges (60%), which was a significant difference (P<0.05) (**Figure 3B**).

DISCUSSION

This is the first reported study that evaluated detailed characteristics of linear furrows in patients with EE. Linear furrows were found to occur in all circumferential directions in a radial pattern and were present in esophageal longitudinal mucosal fold valleys in every patient, whereas none were found on ridges between valleys. In addition, in most cases (81%), these furrows were located widespread throughout the lower to middle or upper esophagus. Although

the pathogenesis of linear furrows remains obscure, possible causes are discussed in detail below.

We speculated that gastroesophageal reflux plays an important role in formation of linear furrows, as gastric acid suppression by PPI administration is effective in more than half of patients with EE. In previous studies, we demonstrated that mucosal breaks seen in RE cases were located on mucosal fold ridges, and mainly found on the right anterior wall of the esophagus.[23,25] In addition, short segment Barrett's esophagus (SSBE) and esophageal adenocarcinoma arising from SSBE, which are thought to be complications of chronic and severe gastroesophageal reflux, have also been frequently reported to occur on the right anterior wall of the esophagus.[26-29] Asymmetrical lower esophageal sphincter pressure may be a major cause of predominant gastroesophageal reflux on the right anterior wall of the distal esophagus and result in mucosal breaks associated with reflux esophagitis, as well as Barrett's esophagus (BE) and BE-associated adenocarcinoma.[24,30,31] In the present study, contrary to our expectation, linear furrows in cases of EE were found in locations different from those of mucosal breaks in cases of RE, suggesting that acid reflux is not directly associated with formation of linear furrows in patients with EE.

Dietary therapy such as an elimination diet for patients with EoE has been shown to reduce symptoms as well as eosinophilic infiltration of the esophagus by reducing antigenic stimulus to the Th2-mediated response.[32] Therefore, direct exposure of antigens to esophageal mucosa may cause characteristic endoscopic findings. Since esophageal mucosa and submucosa form longitudinal folds, and the cross-section of the esophageal lumen is star-shaped,

valleys formed by esophageal mucosa folds are likely to be exposed for longer periods to swallowed antigens as compared to the ridges between valleys. Indeed, eosinophilic infiltration tends to be more intense on mucosa in linear furrows located in those valleys than those on adjacent ridges. Because of the patchy eosinophilic infiltration in the esophageal mucosa, to understand the suitable biopsy location for detection of EE in EoE suspected cases is critically important. We recently reported that the most suitable site for detection of EE was found to be the lower esophagus in association with an endoscopic finding of exudates.[33] Consistent with our findings, Salek et al. have shown that eosinophil peak counts were significantly higher in areas of the esophagus with characteristic endoscopic findings, such as linear furrows and whitish exudates, as compared to normal appearing areas.[34] Therefore, characteristic endoscopic features are now considered to be most important for suspected cases. Although the difference of eosinophilic infiltration in linear furrows between proximal and distal esophagus need to be evaluated, our present results indicate that fewer biopsies from linear furrows should be sufficient for an accurate diagnosis.

In EoE patients, persistent eosinophilic infiltration is associated with tissue remodeling and fibrosis, resulting in decreased esophageal compliance, increased esophageal stiffness, and increased smooth muscle mass with smooth muscle dysfunction.[35,36] These changes may promote not only disease complications, such as esophageal narrowing, rigidity, and strictures, but also gross structural changes, including rings and linear furrows. Kwiatek et al. investigated esophageal wall properties by measuring distensibility using an EndoFLIP® device,[37] and showed that esophageal distensibility was significantly

reduced in EoE patients as compared to control subjects. While traditional esophageal manometry primarily measures the function of circular muscles, Korsapati et al. used an endoscopic ultrasound technique to determine the function of longitudinal muscles,[38] which revealed selective dysfunction of longitudinal muscle contraction during peristalsis in EoE patients. In addition, EoE patients were shown more likely to have abnormal bolus pressurization in the esophagus as compared to GERD patients and control subjects, and early pan-esophageal pressurization after swallowing, which is a manifestation of reduced esophageal compliance, was apparently a specific finding in EoE.[39] Persistent eosinophilic infiltration also impairs mucosal integrity, resulting in an increase in esophageal permeability that allows food antigens to penetrate into deeper layers of the squamous epithelium, where they promote immune activation.[40] Therefore, mucosa in linear furrows that harbors more intense eosinophilic infiltration may be more fragile to radial distention. Taken together, pan-esophageal pressurization with restriction in regard to radial distention and a diffuse loss of elasticity in response to an ingested bolus may cause longitudinal mucosal changes in fold valleys with impaired mucosal integrity. However, the sample sizes in those studies were too small to make clinically significant conclusions, and larger studies are needed to investigate the relationship between esophageal motility dysfunction and symptoms or endoscopic findings in EoE patients.

This study has some limitations. We enrolled patients with EE, including EoE and PPI-REE, as EoE was still rare in Asian populations. Among the 70 enrolled EE patients, only 17 were finally diagnosed with EoE, while 33 with

PPI-REE, and other 20 with indeterminate because of asymptomatic or unfulfilled PPI trial. However, consistent with studies conducted in Western countries,[41-43] the clinical characteristics including endoscopic findings did not differ between EoE and PPI-REE (data not shown). Although further prospective studies are needed to elucidate the mechanism, 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 summary, 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 widespread throughout the lower to middle or upper esophagus. Furthermore, they were only found 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 ≥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.

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CONFLICT OF INTERESTS

Authors declare no conflict of interests for this article.

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Figure legends

Figure 1

Specific locations of linear furrows in patients with esophageal eosinophilia. **A**, **B.** Linear furrows occurred in a radial pattern and were widespread throughout the lower to middle or upper esophagus in most EE cases. White light endoscopy (A). Chromoendoscopy with indigo carmine dye (B). **C**, **D.** Location of linear furrows in relation to esophageal longitudinal folds. The position (valley or ridge) was confirmed using an air-deflated condition. Linear furrows (arrow) were found in esophageal mucosal fold valleys in every patient.

Figure 2

Specific locations of mucosal breaks in patients with reflux esophagitis. **A.** Representative endoscopic findings from mucosal breaks in patients with reflux esophagitis (Grade A, Los Angeles classification). **B.** Circumferential location of mucosal breaks in patients with reflux esophagitis. Mucosal breaks were found on the right anterior wall (from 12 o'clock to 3 o'clock). **C**, **D.** Location of mucosal breaks in relation to esophageal longitudinal folds. The position (valley or ridge) was confirmed using an air-deflated condition. Mucosal breaks (arrow) were predominantly located on mucosal fold ridges.

Figure 3

Relationship between linear furrows and eosinophilic infiltration. **A.** Biopsy specimens were obtained from linear furrows located in valleys (arrow) and on adjacent ridges between the valleys (arrowhead). B. Eosinophilic infiltration

(≥15/HPF) was more frequently found in linear furrows in the valleys as compared to mucosa on adjacent ridges, with a statistically significant difference ($P<0.05$). Lines connecting two dots indicate individual patients. The median is shown by a horizontal bar.

SUPPORTING INFORMATION

Video 1

Representative case showing appearance of linear furrows in a valley between folds in a patient with esophageal eosinophilia.

Video 2

Representative case showing appearance of a mucosal break on a fold ridge in a patient with reflux esophagitis.

Table 1. Clinical characteristics of enrolled patients

Number of patients	70
Male, no. (%)	57 (81)
Age at diagnosis, y, mean ± SD	48.1±14.4
Concurrent allergic disease, no. (%)	50 (71)
Allergic rhinitis	34 (49)
Bronchial asthma	14 (20)
Atopic dermatitis	11 (16)
Food allergy	6 (9)
Symptom, no. (%)	
Dysphagia	37 (53)
Heartburn/regurgitation	22 (31)
Abdominal pain	13 (19)
Laboratory findings, no. (%)	
peripheral eosinophilia	15 (21)
total IgE elevation	28 (40)
H. pylori infection	25 (36)
Endoscopic findings, no. (%)	
Linear furrows	63 (90)
Ring	45 (64)
Whitish exudate	37 (53)
Reflux esophagitis	7 (10)

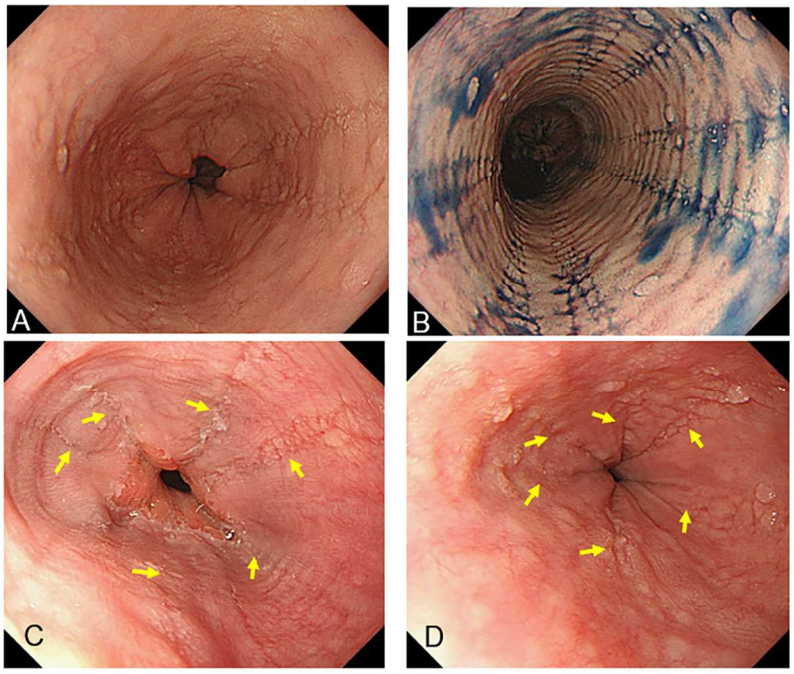

Figure 1
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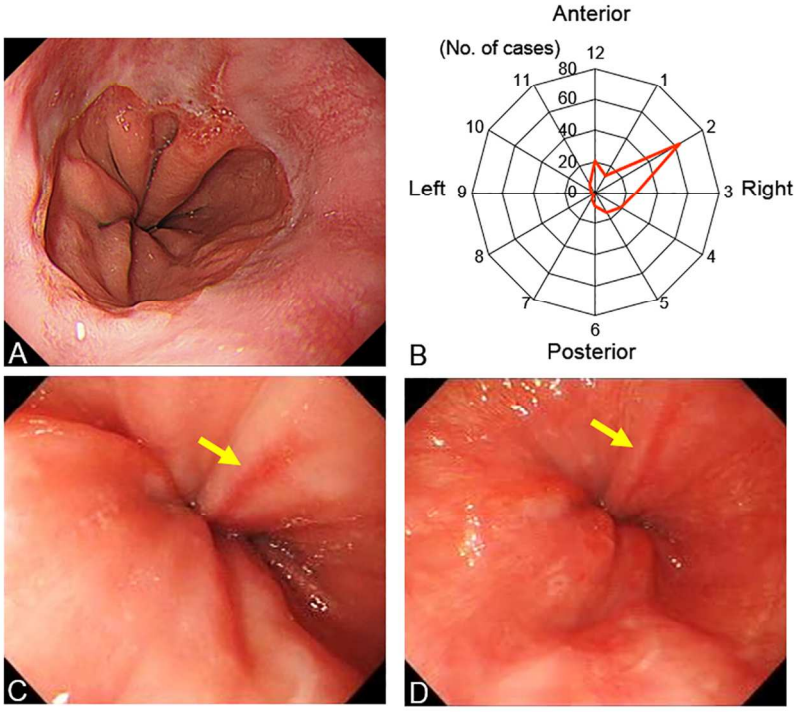

Figure 2
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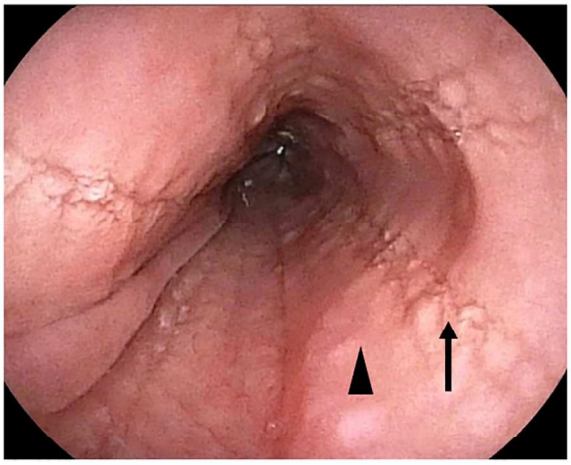

Figure 3A
135x101mm (300 x 300 DPI)

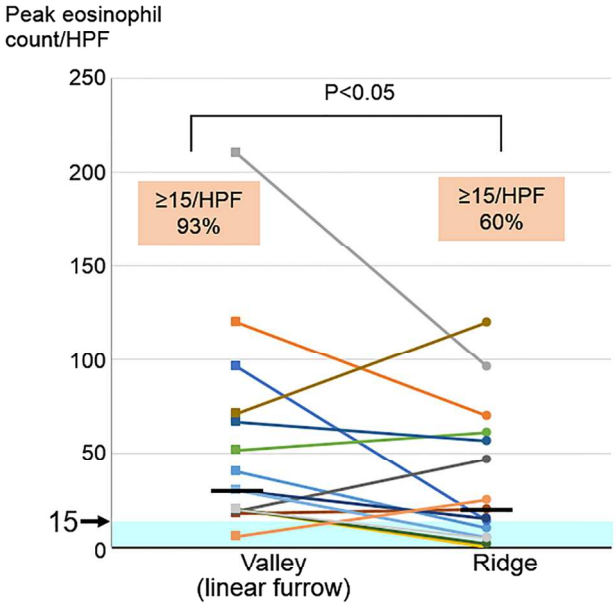

Figure 3B
135x101mm (300 x 300 DPI)