Ankylosaurus back sign: novel endoscopic finding in esophageal eosinophilia patients indicating proton pump inhibitor response

Authors
Norihisa Ishimura1, Shohei Sumi1, Mayumi Okada1, Daisuke Izumi1, Hironobu Mikami1, Eiko Okimoto1, Nahoko Ishikawa2, Yuji Tamagawa1, Tsuyoshi Mishiro1, Naoki Oshima1, Kotaro Shibagaki1, Shunji Ishihara1, Riruke Maruyama2, Yoshikazu Kinoshita1

Institutions
1 Department of Gastroenterology and Hepatology, Shimane University School of Medicine, Izumo, Japan
2 Department of Pathology, Shimane University School of Medicine, Izumo, Japan

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Corresponding author
Norihisa Ishimura, MD, PhD, Department of Gastroenterology and Hepatology, Shimane University School of Medicine, 89-1, Enya-cho, Izumo, Shimane, 693-8501, Japan
Fax: +81-853-20-2187
ishimura@med.shimane-u.ac.jp

ABSTRACT
Background and study aims Characteristic endoscopic findings, such as linear furrows, rings, and whitish exudates, indicate the presence of esophageal eosinophilia (EE), though no specific findings are known to distinguish eosinophilic esophagitis (EoE) from proton pump inhibitor-responsive esophageal eosinophilia (PPI-REE). Here, we present a novel endoscopic finding in some EE patients possessing a linear longitudinal arrangement of whitish nodules with the appearance of the back of an Ankylosaurus dinosaur, termed Ankylosaurus back sign (ABS), and evaluations of its significance in affected patients.

Patients and methods Fifty-five patients diagnosed with EE (≥15 eosinophils/high power field) who were treated at our hospital and shown to evaluate a PPI response were enrolled. Endoscopic findings at baseline and clinical parameters were retrospectively reviewed. Furthermore, the clinicopathological features of patients with ABS, as well as the relationship between its presence and PPI response were evaluated.

Results Fifty-five patients (47 males, 8 females) with EE (17 with EoE, 38 with PPI-REE) were evaluated, of whom 50 (90.9%) had linear furrows, the most frequently found feature, while ABS was found in 9 (16.4%). Inter-observer agreement was substantial for ABS (κ 0.77). Interestingly, all patients with ABS had PPI-REE. Our findings revealed that the presence of ABS was closely associated with reflux esophagitis (RE) in patients with PPI-REE.

Conclusions Although ABS was less frequent than typical endoscopic findings such as linear furrows in EE, this novel finding was closely associated with PPI-REE accompanied with RE. The clinical implications of ABS in patients with EE should be investigated further.

Introduction
Eosinophilic esophagitis (EoE) is characterized by chronic inflammation along with dense eosinophil 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 [1,2]. Pathological identification of esophageal eosinophilia (EE) is considered to be the most important and critical step for diagnosis of EoE. However, the presence of EE is not specific for EoE, thus consensus guidelines require clinical and/or histologic unresponsiveness to acid-suppressive therapy with a proton pump inhibitor (PPI) to exclude other causes of EE, such as gastro-esophageal reflux disease (GERD). In addition, it has become apparent that some patients with a phenotype appearance of EoE and distinct from GERD respond histologically to PPIs. To distinguish them from EoE patients, these are described as having PPI-responsive esophageal eosinophilia (PPI-REE) [3,4].
the other hand, several studies have shown that PPI-REE and EoE are virtually indistinguishable from one another and called into question methods used to make a proper distinction between EoE and PPI-REE [5, 6]. Therefore, the term PPI-REE is retracted and PPI use is recommended for therapeutic agent but not for diagnostic criterion in the most recently updated guidelines [7]. However, the underlying pathogenic mechanism of PPI response for EoE patients remains poorly understood.

The associated endoscopic features of EE and EoE include linear furrows, rings, whitish exudates or plaque, strictures, diffuse narrowing, decreased vascularity or edema, and fragile mucosa (crepe paper appearance) [8, 9], which are increasingly being recognized as signs of EoE. Furthermore, recent prospective studies conducted in both Western and Asian countries have found that at least 1 of these abnormalities is detected by endoscopy in over 90% of examined EoE patients [9–11]. The presence or absence of such endoscopic findings is used to make a diagnosis of EoE, as well as to guide biopsy decisions and assess response to therapy, though no specific endoscopic findings to distinguish EoE from PPI-REE have been presented. Recently, we noted a novel endoscopic finding in some patients with EE, which was recognized as the presence of a linear longitudinal arrangement of whitish nodules, such as the back of an Ankylosaurus dinosaur (Fig. 1), which we termed Ankylosaurus back sign (ABS). However, it remains unknown whether this finding has diagnostic utility for EE. The aim of the current study was to evaluate the significance of ABS in patients with EE and also determine its association with PPI treatment for EE.

Fig. 1 a, b Representative endoscopic findings of Ankylosaurus back sign, defined as a linear longitudinal arrangement of whitish nodules at uniform intervals in the esophagus. a Air deflated condition. b Fully insufflated condition. c Image of Ankylosaurus, a genus of armored dinosaur. (Quelle: AdobeStock_60609420) [rerif]
Patients and methods

Enrolled subjects and data collection

Between July 2013 and January 2016, 70 adult patients with suspected EoE, who had symptoms of esophageal dysfunction and EE, visited our hospital. Histological diagnosis of EE was defined as the presence of ≥15 eosinophils per high power field (HPF) in biopsy samples obtained with endoscopy. Gastric and duodenal biopsy specimens were also collected to exclude concomitant eosinophilic gastroenteritis. 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 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 therapy administered according to current guidelines [3, 4]. Furthermore, PPI-REE was defined as presentation of clinical symptoms similar to those of EoE, with both symptoms and eosinophil infiltration disappearing with PPI treatment at a standard or double dose within 2 months after beginning administration. Of the 70 patient charts initially reviewed, 15 were excluded because of an unfulfilled PPI trial, thus 55 cases were enrolled in this study. The clinical parameters described above were compared between patients with EoE and those with PPI-REE. The protocol of this study was evaluated and approved by the Ethical Committee of Shimane University School of Medicine.

Assessment of endoscopic findings and inter-observer agreement

Images obtained with endoscopy were separately reviewed by 3 expert endoscopists (N.I., E.O., N.O.) to determine the presence and location of ABS, as well as other typical findings including linear furrows, rings, and whitish exudates, in each case. ABS was defined as linear arrangement of whitish nodules with uniform intervals in the esophagus clearly detected by white light endoscopy (Fig. 1a). One of the authors (Y.K.) explained representative endoscopic findings indicating EoE, including ABS before assessment, while endoscopic images used for instruction were not included in this study. The examiners were blinded in regard to the clinical diagnosis of each case and the endoscopic diagnosis was established by consensus of at least 2 of the 3.

To evaluate the reliability of ABS, we estimated the inter-observer agreement for the identification of ABS among these 3 endoscopists. The kappa statistics with 95% confidence interval (CI) were calculated according to Fleiss’ kappa calculation. The kappa value were evaluated as follows: kappa value below 0.20 considered to be poor, 0.21–0.40 fair, 0.41–0.60 moderate, 0.61–0.80 substantial, and 0.81–1.00 almost perfect.

Mucosal breaks in patients with reflux esophagitis (RE) were graded according to the Los Angeles classification. The presence or absence of a hiatal hernia [12], as well as gastric mucosal atrophy [13] were also investigated in each case using endoscopic findings.

Statistical analysis

Statistical analyses were carried out using chi-squared and Mann–Whitney U-tests, with Fisher’s exact test used when necessary. 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

Clinical characteristics of enrolled patients

The 55 enrolled patients consisted of 47 males and 8 females, with a mean (±SD) age of 46.8 ± 13.2 years (range 17–85 years). Of 55 patients with EE, 17 were diagnosed with EoE, while 38 were diagnosed with PPI-REE. The demographic and clinical characteristics of each group are shown in Table 1. The EoE and PPI-REE groups were similar with respect to age (42.0 ± 14.4 vs. 49.0 ± 12.3 years, P = 0.09), gender (males 82.4% vs. 86.8%, P = 0.48), and frequency of concurrent allergic disease (82.4% vs. 78.9%, P = 0.54). In both groups, the most frequently reported symptom was dysphagia (70.6% vs. 50.0%, P = 0.13) and the frequency was not significantly different between them. None of the enrolled patients had a history of food impaction, in contrast to Western EoE patients in whom that frequently occurs [14]. For both the EoE and PPI-REE groups, the number of peripheral eosinophils (17 and 36 cases, respectively) and plasma total IgE level (15 and 28 cases, respectively) were evaluated in most of the patients. There was no significant difference in frequency of peripheral eosinophilia (>500 eosinophil/microliter) (35.3% vs. 22.2%, P = 0.31) or total IgE elevation (>173 IU/mL) (60.0% vs. 60.7%, P = 0.96).

In addition, the rate of Helicobacter pylori (H. pylori) infection, which has been reported to be inversely associated with EoE [15, 16], was not significantly different between the groups (35.3% vs. 31.6%, P = 0.79). Collectively, demographic and clinical features were similar between the present patients with PPI-REE and those with EoE, consistent with our recently reported findings [17].

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 both the EoE and PPI-REE groups (88.2% vs. 92.1%, P = 0.49). Mucosal breaks with grade A or B were also found in both the EoE and PPI-REE groups (11.8% vs. 18.4%, P = 0.43). In contrast, ABS was found in 9 (16.4%) patients with EE. Interestingly, all patients with ABS had PPI-REE. Furthermore, ABS was the only significant parameter to distinguish between the EoE and PPI-REE groups (0% vs. 23.7%, P = 0.03).

Endoscopic and histological features of ABS

Next, we focused on the endoscopic features of ABS in our patients. ABS was found to be positioned in a longitudinal manner, and widespread throughout the lower to middle or upper
esophagus in all cases. Representative endoscopic findings of ABS are shown in ▶ Fig.2a, ▶ Fig.2c, and ▶ Fig.2e. As for circumferential location, ABS was seen in all circumferential directions in a radial pattern in each of these patients. The position of ABS in relation to esophageal longitudinal folds was also assessed. We recently reported that linear furrows were found to be located in mucosal fold valleys in all affected patients [18]. Interestingly, in all of the present patients with ABS, that was found in esophageal longitudinal mucosal fold ridges, where it did not appear in the valleys. In addition, this finding was more clearly observed under an air deflated than fully insufflated condition (▶ Fig. 1a and ▶ Fig.1b).

To assess changes in the characteristics of ABS induced by treatment, specific endoscopic findings obtained after at least 2 months of PPI treatment were evaluated. In all cases with ABS, histological remission of eosinophile infiltration was confirmed following PPI treatment, whereas ABS remained with similar characteristics in 5 of 9 cases with ABS after 2 months of treatment (▶ Fig.2b, ▶ Fig.2d and ▶ Fig.2f). Thereafter, with longer treatment, ABS gradually disappeared in 2 of those 5 cases.

We obtained biopsy specimens from the ABS area in some of the affected patients and representative histological findings of those are shown in ▶ Fig.3. In that representative case, dense eosinophile infiltration (120 eosinophils/HPF) and spongiosis were found in the esophageal epithelial layer. On the other hand, other specific findings were not detected and the histological findings were not different from adjacent mucosa in the valley (data not shown). Therefore, the cause of formation of the whitish nodules remains unclear.

Inter-observer agreement for the identification of ABS
The kappa value of inter-observer agreement for the identification of ABS among 3 endoscopists were 0.77 (95 %CI 0.62–0.92), showing substantial diagnostic agreement. This suggested that ABS could be identified substantially by white light endoscopy as well as other characteristic endoscopic findings for EoE, such as rings, as previously reported [19].

Clinical significance of ABS
Because ABS was only found in patients with PPI-REE, we compared the clinical and endoscopic features between those with PPI-REE and with or without ABS (▶ Table2). All PPI-REE cases positive for ABS (n = 9) were male (mean age 46.3 ± 9.0, range 34–60 years). Clinical data including demographics (age, gender), presenting symptom, concurrent allergic diseases, and laboratory findings were similar between the ABS-positive and -negative PPI-REE cases. As for endoscopic findings, linear furrows were frequently observed in both groups (88.9% vs. 93.1%, P = 0.87). In contrast, whitish exudates were not present in the ABS-positive cases, while that was present in 18 of the 29 ABS-negative cases, a significant difference (0% vs. 62.1%, P = 0.001). Also, mucosal breaks were significantly more frequent

Table 1  Clinical characteristics of patients with EoE and PPI-REE.

|                | EoE patients (n=17) | PPI-REE patients (n=38) | P value |
|----------------|---------------------|-------------------------|---------|
| Age, y, mean ± SD | 42.0 ± 14.4         | 49.0 ± 12.3             | 0.09    |
| Male, no. (%)    | 14 (82.4)           | 33 (86.8)               | 0.48    |
| Concurrent allergic disease, no. (%) | 14 (82.4) | 30 (78.9) | 0.54 |
| Symptom, no. (%) |                     |                         |         |
| dysphagia        | 12 (70.6)           | 19 (50.0)               | 0.13    |
| heartburn/regurgitation | 5 (29.4) | 13 (34.2) | 0.49 |
| Laboratory findings, no. (%) |                     |                         |         |
| peripheral eosinophilia1 | 6 (35.3) | 8 (22.2) | 0.31 |
| total IgE elevation1 | 9 (60.0) | 17 (60.7) | 0.96 |
| H. pylori infection | 6 (35.3) | 12 (31.6) | 0.79 |
| Endoscopic findings, no. (%) |                     |                         |         |
| linear furrows   | 15 (88.2)           | 35 (92.1)               | 0.49    |
| whitish exudates | 10 (58.8)           | 18 (47.4)               | 0.43    |
| rings            | 9 (52.9)            | 28 (73.7)               | 0.13    |
| ABS              | 0 (0)               | 9 (23.7)                | 0.03    |
| Reflux esophagitis | 2 (11.8) | 7 (18.4) | 0.43 |

1 Peripheral eosinophil count and total IgE were not evaluated in all of the enrolled subjects. EoE, eosinophilic esophagitis; PPI-REE, proton pump-inhibitor responsive esophageal eosinophilia; ABS, Ankylosaurus back sign
in the ABS-positive group (55.6% vs. 6.9%, $P = 0.004$), suggesting that the presence of ABS is closely associated with gastric acid reflux in patients with PPI-REE.

**Discussion**

This is the first known study to present and evaluate a novel endoscopic finding, termed ABS, in patients with EE. To date, several characteristic endoscopic findings, including linear furrows, rings, and whitish exudates, have been reported as useful
for diagnosis of EoE [18, 20, 21]. In addition, a new classification system to standardize the endoscopic assessment of esophageal signs of EoE (EREFS) was recently introduced [8]. This classification consists of the 5 most common and reproducibly identifiable findings, including edema (or decreased vascular- ity), rings, exudates, furrows, and strictures. EREFS has been va- lidated in studies performed in Western countries, and shown to have usefulness for diagnosis as well as monitoring treat- ment response in patients with EoE [19, 22, 23]. In addition, several minor endoscopic findings have been reported, such as esophageal polyps [24–26] and cobblestone-like appearance [27]. ABS also features nodular formation, though the linear ar- rangement occurs at uniform intervals and is completely differ- ent from those previously reported findings.

The prevalence of EoE has been rapidly increasing in both Western and Asian countries, including Japan [10, 28], leading to increased recognition of characteristic endoscopic findings among Japanese endoscopists. According to a recent systematic review, linear furrows are the most frequently reported ab- normality in Asian patients with EoE [10]. Although most typical endoscopic findings reported in studies conducted in West- ern and Asian countries are similar, there may be ethnic differ- ences in regard to EoE-related endoscopic findings. For exam- ple, as compared with Caucasian patients, Asians rarely have stenotic-type endoscopic findings, such as strictures or diffuse narrowing, which are associated with food impaction, a typical symptom of Western EoE patients, suggesting that the clinical presentation of EoE in Asian patients might be milder. We spec- ulate that ABS may be a finding specific for Asian patients.

Nonetheless, a large scale multi-center study is needed to con- firm the precise prevalence of this finding in EE and EoE cases.

In the current study, we evaluated detailed endoscopic fea- tures of ABS in our patients. ABS was found to occur in all circumferential directions in a radial pattern and appeared in esophageal longitudinal mucosal fold ridges in every affected patient, whereas none were found in valleys between ridges. Since esophageal mucosa and submucosa form longitudinal folds, and the cross-section of the esophageal lumen is star- shaped, positioning in relation to esophageal longitudinal folds (ridge or valley) may be important in regard to the pathogen- esis of ABS. In previous studies, we demonstrated that mucosal breaks seen in RE cases were located on mucosal fold ridges, mainly on the right anterior wall of the esophagus [18, 29]. The mucosal breaks found on esophageal fold ridges in patients with RE suggest a more pronounced effect of refluxed gastric acid on those ridges. Therefore, the preferential presence of ABS on the fold ridges indicates a possible role of refluxed acid for its formation. In addition, awareness of the localization of ABS on esophageal fold ridge with air deflated condition can help to detect lesions during endoscopic procedures. Indeed, ABS was able to be identified with substantial inter-observer agreement among expert endoscopists after instruction re- garding the endoscopic characteristics of ABS.

ABS was found only in patients with PPI-REE in the current study. Moreover, mucosal breaks suggesting increased gastric acid reflux were more frequently found in the ABS-positive PPI-REE group. These findings indicate that gastroesophageal reflux may play an important role in formation of ABS. While, ABS was

| Table 2 Clinical characteristics of patients with PPI-REE with/without ABS. | ABS-positive PPI-REE (n = 9) | ABS-negative PPI-REE (n= 29) | P value |
|---|---|---|---|
| Age, y, mean ± SD | 46.3 ± 9.0 | 49.8 ± 13.2 | 0.38 |
| Male, no. (%) | 9 (100) | 24 (82.8) | 0.24 |
| Concurrent allergic disease, no. (%) | 6 (66.7) | 24 (82.8) | 0.28 |
| Symptom, no. (%) | | | |
| dysphagia | 5 (55.6) | 14 (48.3) | 0.50 |
| heartburn/regurgitation | 3 (33.3) | 10 (34.5) | 0.61 |
| Laboratory findings, no. (%) | | | |
| peripheral eosinophilia | 2 (22.2) | 6 (22.2) | 0.69 |
| total IgE elevation | 3 (37.5) | 14 (70.0) | 0.12 |
| H. pylori infection | 4 (44.4) | 8 (27.6) | 0.91 |
| Endoscopic findings, no. (%) | | | |
| linear furrows | 8 (88.9) | 27 (93.1) | 0.87 |
| whitish exudates | 0 (0) | 18 (62.1) | 0.001 |
| rings | 7 (77.8) | 21 (72.4) | 0.56 |
| Reflux esophagitis | 5 (55.6) | 2 (6.9) | 0.004 |

1 Peripheral eosinophil count and total IgE were not evaluated in all of the enrolled subjects. ABS, Ankylosaurus back sign; PPI-REE, proton pump-inhibitor responsive esophageal eosinophilia; H. pylori, helicobacter pylori
not found localized on the right anterior wall, and did not disappear after 2 months of PPI administration, despite confirmation of remission of eosinophil infiltration shown by histological findings. Persistent eosinophil 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 [30, 31]. Although no specific histological findings were detected in biopsied esophageal epithelium samples in the present cases, subepithelial fibrosis may be associated with formation of whitish nodules associated with ABS in the esophagus. Endoscopic ultrasonography may be useful to clarify the pathogenesis of ABS.

A recent systematic review revealed that approximately half of investigated patients with symptomatic EE showed findings suggestive of histological remission of EE achieved with PPI therapy [32]. Currently, EE and PPI-REE remain indistinguishable without administration of PPI therapy, and there is concern regarding whether these should be considered as different diseases, especially when considering that they share similar or nearly identical genetic, phenotypic and mechanistic features [17, 33]. Therefore, PPI therapy should be considered as the first step, with diet/steroid treatment representing a further step up in therapy in the absence of clinical or histological response to PPI therapy as recommended in the updated guidelines [7]. PPI use is generally considered to be safe, though there is increasing information showing the potential of adverse effects with prolonged exposure to the drugs [34, 35]. To reduce that concern, factors associated with favorable PPI response in patients with EE should be clarified. We consider that ABS may identify a PPI responsive phenotype of EE, as it was found only in patients with PPI-REE.

This study has some limitations. It was performed in a retrospective manner at a single tertiary referral center. Also, the number of patients with EE may not be adequate to compare with PPI-REE patients in regard to clinical characteristics, because of the lower number of cases in Asian populations. All the endoscopic images were based on still images, which may differ from the real-time endoscopic assessment. In addition, this finding may be subjective nature of the sign, and was different from the real-time endoscopic assessment. In the present cases, subepithelial fibrosis may be associated with formation of whitish nodules associated with ABS in the esophagus. Endoscopic ultrasonography may be useful to clarify the pathogenesis of ABS.

In summary, we report a new endoscopic feature termed ABS, which was found in 16.4% of patients with EE. Although ABS was less frequent than typical endoscopic findings such as linear furrows in those patients, it was closely associated with PPI-REE accompanied with RE. Further studies are needed to investigate the clinical implications of ABS in patients with EE.

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Competing interests

None

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