Usefulness of the Eosinophilic Esophagitis Histologic Scoring System in Distinguishing Active Eosinophilic Esophagitis From Remission and Gastroesophageal Reflux Disease

Bo Lin\textsuperscript{a, b}, Simon Rabinowitz\textsuperscript{c}, M.A. Haseeba\textsuperscript{b, d}, Raavi Gupta\textsuperscript{a, e}

Abstract

Background: Eosinophilic esophagitis (EoE) is defined as esophageal dysfunction in the presence of > 15 intraepithelial eosinophils per high-power field (eos/hpf) in either the mid or distal esophagus. The current focus of EoE pathologic evaluation is the peak eosinophil count (PEC), although histologic features other than eosinophilic inflammation are also commonly observed. In addition, histologic variance between the mid and distal esophagus in EoE has not been rigorously studied. The aim of our study was to utilize a recently developed EoE histologic scoring system (EoEHSS) to compare the mid and the distal esophageal histology in patients with active EoE (EoE-A), EoE in remission (EoE-R), and gastroesophageal reflux disease (GERD).

Methods: EoEHSS was used to prospectively evaluate the severity and extent of changes in multiple histopathologic features (PEC; basal zone hyperplasia (BZH); eosinophilic abscesses (EA); eosinophil surface layering (ESL); dilated intercellular spaces (DIS); surface epithelial alteration (SEA); dyskeratotic epithelial cells (DEC); lamina propria fibrosis (LPF)) in the mid and distal esophageal biopsies in 85 pediatric patients at a tertiary medical center. These patients were divided into three cohorts: EoE-A (n = 36), EoE-R (n = 12) and GERD (n = 37).

Results: Total grade (severity) and stage (extent) scores were significantly higher in EoE-A compared to EoE-R and GERD patients in both the mid and the distal esophagus. The mean total grade scores in the mid esophagus, but not the distal esophagus remained higher in EoE-R as compared to GERD patients. Specific histopathologic features independent of PEC were different in distal and mid esophagus in EoE-A. About one-half of children with active EoE had different EoEHSS scores in their mid and distal esophageal biopsies.

Conclusions: EoEHSS yields histologic insights beyond those derived from PEC and helps in more objective, reproducible and accurate diagnosis of EoE and GERD. It also provides a more comprehensive understanding into the pathophysiology of EoE.

Keywords: Eosinophilic esophagitis; EoEHSS; Peak eosinophil count

Introduction

Eosinophilic esophagitis (EoE) is a clinicopathological condition defined clinically by non-specific manifestations of esophageal dysfunction in young children, and dysphagia and food impaction in older adolescents, in the presence of > 15 intraepithelial eosinophils per high-power field (eos/hpf) [1-3]. Esophageal eosinophilia itself is a relatively non-specific finding, and the diagnosis of EoE requires a close correlation between clinical findings and histopathological features [2, 4]. Although esophageal eosinophilia is seen in a variety of diseases, the principal mimic of EoE is gastroesophageal reflux disease (GERD) [5, 6]. Histologically, GERD is characterized by mild to moderate eosinophilia generally localized to the distal esophagus. EoE often also includes mid esophageal eosinophilia, superficial eosinophilic abscesses (EA), degranulation of eosinophils, submucosal fibrosis, and deeper involvement of the esophageal wall [5, 6]. Clinical symptoms such as dysphagia and heartburn can be seen in both conditions; therefore, it can sometimes be a clinical challenge to differentiate EoE and GERD [7].

The current focus of evaluating esophageal biopsies in patients with suspected EoE is the severity of eosinophilic infiltration, i.e., peak eosinophil count (PEC). Reduced PEC constitutes an endpoint in clinical trials of therapies for EoE and is a universal goal in clinical management [4]. Several previous investigators have attempted to identify additional
histologic features that would further characterize EoE [8-10]. Microabscesses, superficial layering, surface sloughing, desquamation, and degranulation have been observed more commonly in patients with EoE than those with GERD [8]. Other more comprehensive scoring systems to evaluate EoE have been proposed. These have uniformly included several “core features”: eosinophil microabscesses, basal zone hyperplasia (BZH), dilated intercellular spaces (DIS), and lamina propria fibrosis (LPF) [8-10]. Subsequently, additional features were introduced to compare two clinical subgroups of EoE: EoE-dysphagia (EoE-D) and EoE-abdominal pain (EoE-AP). Microabscesses, superficial layering of eosinophils, desquamation, and eosinophilic distribution around rete pegs were found to be significantly more common in EoE-D than EoE-AP [9].

A slightly different scoring system was created to account for eosinophils in the epithelium and lamina propria, basal zone hyperplasia, dilated intercellular spaces, desquamation and lamina propria fibrosis to evaluate EoE [10].

A recently published EoE histologic scoring system (EoEHSS) employs eight histologic features including: PEC; BZH; EA; eosinophil surface layering (ESL); DIS; surface epithelial alteration (SEA); dyskeratotic epithelial cells (DEC); and lamina propria fibrosis (LPF). Each feature is assigned two scores: grade (severity) and stage (extent) using a four-point Linkert scale [11]. This scoring system was able to distinctly identify untreated and treated EoE patients based on grade and stage scores. Subsequently, other investigators have independently established the value of EoEHSS [12]. It is now recognized as the most valid, reliable index currently available for measurement of histological disease activity in EoE [13]. The present study employs a novel application of the EoEHSS in which the total grade and stage scores were compared among the cohorts for both mid and distal esophagus.

EoEHSS grade and stage scores are different between EoE-A, EoE-R and GERD.

**Materials and Methods**

**Patient groups**

Eighty-five patients with suspected, diagnosed, and treated EoE were enrolled in a prospective study at a tertiary care center. Parents of children under 18 years and patients who were 18 years old consented and children above 7 years assented prior to participation. Patients were divided into three cohorts: 1) EoE-A diagnosed by consensus guidelines [14] (n = 36; 76 esophageal biopsies, 39 distal, 37 mid), including proton pump inhibitor (PPI) non-responders; 2) EoE patients who received treatment with PPI, dietary exclusion, and topical steroids that yielded clinical and histopathologic remission defined as < 15 eosinophils/hpf in at least six biopsies from the mid and distal esophagus (EoE-R) (n = 12; 24 esophageal biopsies, 12 distal, 12 mid); and 3) control patients who underwent endoscopy for evaluation of esophageal symptoms, but had neither endoscopic or histologic features of EoE, and GERD accounted for their esophageal dysfunction (n = 37; 74 esophageal biopsies, 37 distal, 37 mid). Majority of the patients with EoE had a history of asthma or atopic conditions as part of the disease spectrum, and none of the participants reported smoking.

This study was conducted in compliance with the ethical standards of the institution on human tissue, and it was approved by the Institutional Review Board and Privacy Board (IRB) of the State University of New York Downstate Medical Center (IRB: 703018-5).

**EoEHSS scoring**

Eight histologic features as described in EoEHSS were identified and scored at mid and distal esophagus separately [11]. These features include: PEC; BZH; EA; ESL; DIS; SEA; DEC; and LPF. Each feature was quantitatively assigned grade (severity) and stage (extent) scores using a four-point scale (0 normal; 3 maximum change). Total grade and stage scores were calculated and compared among the cohorts for both mid and distal esophagus.

Severity of PEC was categorized into three groups: low < 15 eos/hpf, moderate 15 - 59 eos/hpf and high > 60 eos/hpf as has been previously described [11]. The extent of eosinophils was categorized as low (involving < 1/3 of epithelium), moderate (involving 1/3 to 2/3 of epithelium) and high (involving > 2/3 of epithelium).

Two of authors (BL and RG) independently evaluated the biopsies and for the few cases with different scores, consensus was reached through mutual agreement.

**Statistical analysis**

Data were analyzed using SPSS (v. 18.0). Mann-Whitney U test was used to compare the scores between cohorts and P < 0.05 was considered statistically significant. Pearson correlation coefficient test was used to compare the severity and extent of PEC and the total grade and stage scores, respectively.

**Results**

**Demographics**

There were 60 males and 25 females, and their median age was 10.2 years (range: 1 - 21 years) at the time of endoscopy. Thirty-seven patients diagnosed with GERD who served as controls had a median age of 11 years (range: 1 - 21 years) and a male/female ratio of 1.3:1. Thirty-six patients had EoE-A with a median age of 9.5 years (range: 1 - 20 years) and a male/ female ratio of 4:1. Twelve patients with EoE-R had a median age of 10.5 years (range: 2 - 21 years) and a male/female ratio of 5:1 (Table 1).
1a). The mean total grade scores were similar between the mid and distal biopsies in EoE-A patients (P > 0.05). In EoE-R and GERD patients, the mean total grade score at distal esophagus is similar (P > 0.05); however, it is significantly higher at mid esophagus in EoE-R patients (P < 0.05) (Fig. 1a). The grade scores of individual features assessed were significantly higher in the EoE-A patients as compared to those with EoE-R or GERD (Table 2).

Mean total stage scores were significantly higher in patients with EoE-A compared to patients with EoE-R or GERD at both mid and distal esophageal sites (P < 0.001, for both sites and both groups). The stage scores were similar between the mid and distal esophagus in the EoE-A patients (P > 0.05) (Fig. 1b). The mean total stage scores were similar between EoE-R and GERD patients in both the mid and distal esophagus (Fig. 1b).

**EoEHSS grade and stage scores correlate with the severity and extent of PEC**

PEC severity (r = 0.781) and extent (r = 0.68) correlated with the mean total grade and stage scores respectively in EoE-A (Fig. 2a, b). EoE-A patients with low PEC severity and extent still had significantly higher total grade and stage scores compared to EoE-R and GERD patients. There was no difference in PEC between mid and distal esophagus in EoE-A patients (P > 0.05). There was no difference in PEC at mid and distal esophagus, between the EoE-R and GERD patients (P > 0.05); both were low.

**Histopathologic differences are present between the mid and distal esophagus in EoE-A**

The mean grade score for each of the eight individual features of the EoEHSS was higher in EoE-A compared to EoE-R and GERD (all P < 0.05). Grade scores for BZH and DIS were independent of PEC and were significantly higher in the distal compared to mid esophagus in EoE-A (both P < 0.05) (Fig. 3a). Mean PEC did not differ between distal and mid esophagus in these cases (P > 0.05). LPF was more severe in mid than distal esophagus (few biopsies with adequate

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**Table 1. Characteristics of Patients With GERD, EoE-A and EoE-R**

| Patient groups | GERD (n = 37) | EoE-A (n = 36) | EoE-R (n = 12) |
|---------------|--------------|----------------|---------------|
| Age, median (range), years | 11 (1 - 21) | 9.5 (1 - 20) | 10.5 (2 - 21) |
| Gender | | | |
| Male | 21 | 29 | 10 |
| Female | 16 | 7 | 2 |
| PEC/hpf, mean ± 1 SEM | 0.5 ± 0.24 | 66 ± 6.7 | 1.5 ± 0.7 |

hpf: high-power field; PEC: peak eosinophil count; SEM: standard error of mean; GERD: gastro-esophageal reflux disease; EoE-A: active eosinophilic esophagitis; EoE-R: eosinophilic esophagitis in remission.

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![Figure 1. Total grade scores (a) and total stage scores (b) in patients with gastroesophageal reflux disease (GERD), active eosinophilic esophagitis (EoE-A) and eosinophilic esophagitis in remission (EoE-R) in distal and mid esophagus. Horizontal lines above the bars show the groups that were compared and had a significant difference (P < 0.05).](image-url)
submucosal tissue were available for analysis) (Fig. 3a). The mean stage scores of BZH, DIS, LPF and PEC in EoE-A patients were not significantly different between mid and distal esophagus (Fig. 3b).

**Discordance is common between mid and distal esophageal EoEHSS scores in EoE-A**

In patients with EoE-A, 18/36 (50%) had four-point difference in EoE grade scores and 20/36 (56%) had four-point difference in stage score between the distal and mid esophagus. Of these patients with discordant scores, 15 patients showed disparity in both the grade and stage scores. Remaining five patients had disparity in only the stage score and three patients had disparity in only the grade score. Of the 18 patients with grade score disparities between mid and distal esophagus, six had higher scores in the mid esophagus and 12 had higher scores in the distal esophagus. Of the 20 patients with stage score disparities between mid and distal esophagus, eight had higher stage scores in the mid esophagus while 12 had higher scores from their distal biopsies (Table 3).

As the EoEHSS scores for EoE-R and GERD were substantially lower in both the mid and distal esophagus, no sig-

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**Table 2. Mean Grade and Stage Scores of Histologic Features of Patients With GERD, EoE-A and EoE-R**

| Histologic feature                  | GERD (n = 37) | EoE-A (n = 36) | EoE-R (n = 12) |
|-------------------------------------|--------------|---------------|---------------|
| Peak eosinophil count/hpf           | 1 ± 0        | 2.2 ± 0.09    | 1 ± 0         |
| Basal zone hyperplasia              | 0.0 ± 0.03   | 2.1 ± 0.12    | 0.25 ± 0.09   |
| Eosinophil abscesses                | 0            | 0.8 ± 0.13    | 0             |
| Eosinophil surface layering         | 0            | 0.8 ± 0.13    | 0             |
| Dilated intercellular spaces        | 1.1 ± 0.04   | 2.5 ± 0.07    | 1.3 ± 0.09    |
| Surface epithelial alteration       | 0            | 0.8 ± 0.14    | 0.8 ± 0.13    |
| Dyskeratotic epithelial cells       | 0            | 0.1 ± 0.04    | 0             |
| Lamina propria fibrosis             | 0.1 ± 0.04   | 1.6 ± 0.16    | 0.5 ± 0.1     |

Data are expressed as mean ± 1 SEM. hpf: high-power field; SEM: standard error of mean; GERD: gastroesophageal reflux disease; EoE-A: active eosinophilic esophagitis; EoE-R: eosinophilic esophagitis in remission.

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**Figure 2.** Total grade scores (a) and total stage scores (b) in patients with gastroesophageal reflux disease (GERD), active eosinophilic esophagitis (EoE-A) relative to PEC (high (EoE-A-H), moderate (EoE-A-M), low (EoE-A-L)) and eosinophilic esophagitis in remission (EoE-R). Horizontal lines above the bars show the groups that were compared and had a significant difference (P < 0.05).

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significant deviations in histopathologic features were noted in these two cohorts.

Discussion

The present study corroborates that EoEHSS is a reproducible diagnostic score to evaluate histologic features of esophageal biopsies of EoE patients. EoEHSS in our patient cohort yielded significantly higher grade and stage scores in EoE-A compared to patients with EoE-R or GERD. Our study confirms a positive correlation between PEC and the total grade and stage scores in EoE-A patients. The clinical value of introducing EoEHSS in routine clinical practice is supported by the observation that PEC, the histologic hallmark presently employed to characterize EoE, does not always correspond to the extent of tissue injury, as the eosinophils may resolve in EoE-R; however, tissue injury is still present in the mid esophagus.

The present study employs a novel application of EoEHSS, to compare mid and distal esophageal scores in patients with EoE-A, EoE-R, and GERD. In our cohort, the mean total grade (severity) scores in the mid esophagus, but not in the distal esophagus, of EoE-R patients remained above the baseline noted in GERD. Thus, the EoEHSS (unlike the PEC) highlights for the first time a divergence in the histologic recovery between mid and distal esophagus in EoE patients that have resolved their clinical symptoms and tissue eosinophilia. If established in larger cohorts, this would suggest that full resolution of esophageal remodeling in EoE may require a longer period of recovery after eosinophilia has resolved.

EoEHSS also establishes a more comprehensive understanding of EoE histology by analyzing individual features associated with EoE that are independent of PEC, such as BZH, DIS and LPF. BZH and DIS were more prominent in the distal esophagus compared to the mid esophagus in our EoE-A cohort, whereas LPF was more severe in the mid than distal esophagus in this group. This difference is not reflected when comparing mid and distal PEC, extending the utility of using EoEHSS to provide insights beyond those derived from simply counting eosinophils. A similar conclusion was reached in another study that found that BZH has a higher correlation with the transcriptome expression in active EoE than PEC [15].

Total and individual EoEHSS scores frequently varied between the mid and distal esophagus in a single patient with EoE-A, not always higher in distal esophagus. This variation in severity between mid and distal esophagus could present as different clinical symptoms, correspond to distinct EoE subtypes, represent variations in responses to different antigens, or to different treatment approaches.

Our study has several limitations. The patient cohorts are relatively small in number and all patients are from a single institution which serves patients from a limited geographic area. Larger diverse cohorts may be required to confirm the observations made in our study. The definition of EoE-R of < 15 eos/hpf is widely utilized but some investigators have recently proposed a cutoff of < 5 eos/hpf. As the guidelines are continuously being revised, further studies with updated criteria may be helpful in better understanding of the disease.

In summary, EoEHSS was successfully applied to evaluate the difference in mid and distal esophagus in patients with EoE-A, EoE-R, and GERD. EoEHSS scores in mid and distal esophagus were significantly higher in children with EoE-A compared to patients with EoE-R or GERD. EoEHSS in our patient cohort yielded significantly higher grade and stage scores in EoE-A compared to patients with EoE-R or GERD. The clinical value of introducing EoEHSS in routine clinical practice is supported by the observation that PEC, the histologic hallmark presently employed to characterize EoE, does not always correspond to the extent of tissue injury, as the eosinophils may resolve in EoE-R; however, tissue injury is still present in the mid esophagus.

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Table 3. Grade and Stage Scores of Histologic Features for Mid and Distal Esophageal Regions in EoE-A Patients

|                | Distal = Mid | Distal > Mid | Distal < Mid |
|----------------|--------------|--------------|--------------|
| Grade score    | 18 (50%)     | 12 (33.3%)   | 6 (16.7%)    |
| Stage score    | 16 (44.4%)   | 12 (33.3%)   | 8 (22.2%)    |

Data are expressed as n (%). EoE-A: active eosinophilic esophagitis.
compared to EoE-R and GERD. As EoEHSS identified discordance in mid and distal esophagus pathology in both EoEA and EoE-R, it emphasizes the importance of obtaining tissue from both sites, as has been recommended in the clinical guidelines [14]. Our study concluded that features of active EoE, independent of PEC, often vary between mid and distal esophagus and that healing may not be uniform in the entire esophagus. EoEHSS helped quantitate disease activity beyond those derived from PEC, and thus provided a more comprehensive understanding into the pathophysiology of EoE. We propose using EoEHSS in daily clinical practice as it will help make the diagnosis of EoE more objective, reproducible and accurate and better understand the pathophysiology of EoE.

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Conflict of Interest

The authors declare that there is no conflict of interest.

Informed Consent

All subjects provided written informed consent.

Author Contributions

BL, SR, RG and MAH designed the study. BL, SR and RG conducted the study. BL, SR and MAH wrote the manuscript. All authors reviewed and edited the manuscript.

Data Availability

The data supporting the findings of this study are available within the article.

Abbreviations

BZH: basal zone hyperplasia; DIS: dilated intercellular spaces; DEC: dyskeratotic epithelial cells; EA: eosinophil abscesses; EoE: eosinophilic esophagitis; EoEHSS: eosinophilic esophagitis histologic scoring system; ESL: eosinophil surface layering; GERD: gastroesophageal reflux disease; LPF: lamina propria fibrosis; PEC: peak eosinophil count; SEA: surface epithelial alteration

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