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Histologic similarities in children with eosinophilic esophagitis and PPI-responsive esophageal eosinophilia

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Capsule Summary:

The EPX histologic scoring system can be used to differentiate children with EoE and PPI-REE relative to GERD, supporting the relationship between these 2 groups and enhancing current diagnostic and treatment approaches.

Keywords

Eosinophilic Oesophagitis; Pediatric; Eosinophil peroxidase; Eosinophil granule protein; Gastroesophageal Reflux Disease; Degranulation; Tissue biomarker

To the Editor:

Distinguishing between eosinophilic esophagitis (EoE), gastroesophageal reflux disease (GERD), and proton pump inhibitor-responsive esophageal eosinophilia (PPIREE) is difficult because symptoms overlap and there is no pathognomonic histologic feature for these disorders(1). Current EoE diagnostic guidelines define EoE as a clinicopathological

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condition characterized by symptoms of esophageal dysfunction and > 15 eosinophils per high power field (eos/HPF) in the esophageal mucosa after ruling out other etiologies as a cause of inflammation(1). Treatment with high-dose proton pump inhibitors (PPI) had been used in clinical practice to exclude GERD and distinguish it from EoE(1). However, recent studies suggest that PPI-REE may represent a subset of patients with EoE(2), suggesting that PPIs should be considered as treatment for EoE, rather than simply part of the diagnostic algorithm. Enumeration of eosinophils using Hematoxylin & Eosin (H&E) stained biopsy sections may underestimate the extent of eosinophil involvement including features such as degranulation. We previously developed a histologic scoring system that assessed eosinophil peroxidase (EPX) to differentiate adults with EoE from GERD(3). The EPX scoring system differentiates intact eosinophils from eosinophil degranulation, as well as quantifying tissue distribution patterns of eosinophilia(3). The aim of this study was to assess the ability of the EPX scoring system to identify similarities and differences in the pattern of eosinophilic inflammation between EoE, PPI-REE and GERD in children. We hypothesized that children with EoE and PPI-REE would have similar EPX scores, whereas children with GERD would have lower scores.

We conducted a retrospective case control study of pediatric subjects cared forat Children's Hospital Colorado between 2006 and 2016 with EoE, PPI-REE, GERD and normal controls (Table). Subjects with EoE were defined according to consensus recommendations(1). Subjects with PPI-REE had ≥ 15 eos/HPF and were symptomatically and histologically responsive to high dose PPI (1–2 mg/kg/day). Subjects with EoE or PPI-REE, selected for this study, demonstrated histologic resolution of esophageal eosinophilia (< 15 eos/HPF) after 6–8 weeks of their prescribed treatment. Control subjects had gastrointestinal symptoms necessitating upper intestinal endoscopy with normal histology. Immunohistochemical staining with an EPX monoclonal antibody and scoring was performed as previously described(3). Briefly, this algorithm assesses 5 features: 1) maximum eosinophils in a single focus; 2) average number of eosinophils in five 40X high power fields; 3) level of degranulation; 4) patchiness or the extent of eosinophil infiltration and degranulation in the maximally affected biopsy; and 5) reproducibility or the extent of all biopsies with eosinophil infiltration or degranulation. The magnitude of each feature is assessed, along with a priority factor for each feature that gives a single numeric value to the global characteristics of tissue eosinophilia. (**see** Supplementary Table **in this article's Online Repository at** www.jacionline.org). Paired post-treatment esophageal biopsies were available for EoE and PPI-REE subjects. This study was approved by the Institutional Review Board at Children's Hospital Colorado (IRB 07–0888). Statistical analysis of data was performed by one-way analysis of variance with Tukey's Post-hoc test and a P-value < 0.05 was considered statistically significant. GraphPad Prism 7 (GraphPad Software, LaJolla CA) was used for statistical analysis.

Paired biopsies, pre- and post-therapy, were analyzed for EoE (n=24) and PPIREE (n=9) subjects, while single biopsies were analyzed for GERD (n=28) and control (n=22) subjects. EoE patients were treated with swallowed topical corticosteroids (n=10), elimination diet (n=7), or a combination of both (n=7). The patient demographics, peak eosinophil count as measured by H&E and endoscopic findings for each group are as shown in the Table.

Treatment of EoE, with dietary elimination or topical corticosteroids, led to significant decreases in each individual parameter of the EPX histologic score (including reproducibility, patchiness, degranulation, max eosinophilic infiltrate in single focus, and average eosinophilic infiltrate), and in the total EPX score (42.0±1.7 vs 5.1±2.1, $P<0.0001$) (**See** Figure). Similarly, PPI therapy in PPIREE subjects also led to significant decreases in all parameters including total EPX score (40.3±2.5 vs 4.6±2.3, $P<0.0001$). No statistically significant differences were found when comparing EPX scores for EoE and PPI-REE before treatment, but EPX scores were significantly elevated in both groups compared to GERD (EoE pre-treatment vs GERD, 42.0±1.7 vs. 2.7±1.4, $P<0.0001$; PPI-REE pre-treatment vs GERD, 40.3±2.5 vs. 2.7±1.4, $P<0.0001$). Thus, PPI-REE and EoE scores were comparable but both uniquely discernible from GERD.

During the last decade, an accumulating body of evidence supports the view that a proportion of patients with clinical features (i.e. symptoms and endoscopic features) and histopathologic findings (i.e. mucosal eosinophilia and molecular analytes) consistent with EoE respond to PPI(2). In addition to acid-protective effects, PPIs have anti-inflammatory properties related to inhibition of eotaxin-3, a chemoattractant involved in the pathogenesis of EoE(4). As a result, up to 50% of patients with histologic findings consistent with EoE may respond to PPI therapy(5).

Previous studies have evaluated the utility of staining the esophageal epithelium for markers associated with EoE, including major basic protein, eotaxin-3, and tryptase in adults, and found that these markers are higher in EoE, but do not differentiate between EoE and PPI-REE(6). Additionally, studies found that tryptase and EPX staining may aid in differentiating between EoE and GERD in adults(3, 7). Our study sought to compare eosinophilic inflammation in EoE and PPI-REE with a previously described EPX immunohistochemical scoring system. Consistent with prior studies, the results demonstrate that eosinophilic inflammation in PPI-REE and EoE are similar pre and post-treatment. Our results also suggest that EPX staining in these two groups is different from GERD. One important strength of this study was inclusion of treatment naïve, PPI-REE subjects; a population often excluded in other studies due to the previous diagnostic algorithm, however, we acknowledge the limitation of the small sample size of PPI-REE group. Recently published updated consensus recommendations suggesting that PPIs may serve as treatment for EoE could allow future studies to identify a larger number of subjects who are PPI-naïve(2). Another limitation is that subjects with GERD had lower peak eosinophil counts than EoE and PPI-REE subjects. Previous studies have shown that esophageal eosinophil counts alone do not distinguish EoE and GERD subjects with GERD may have > 15 eos/HPF; however, this degree of eosinophilic inflammation in GERD is usually associated with erosive or microscopic esophagitis. The present study was conducted in pediatric subjects where erosive or microscopic esophagitis are less common.

With the emergence of an increasing number of methods to assess the esophagus in patients with EoE, enumeration of eosinophils in biopsies as the sole metric for inflammation may be limiting. The EPX scoring system assesses eosinophilic infiltration, density, distribution, and degranulation. An EoE Histologic Scoring System (EoEHSS) was recently developed by *Collins et al* to evaluate other pathologic features in esophageal biopsies from patients with

EoE including basal zone hyperplasia, eosinophil abscesses, eosinophil surface layering, dilated intercellular spaces, surface epithelial alteration, and dyskeratotic epithelial cells.(8) Although the EoEHSS evaluates additional pathologic features beyond peak eosinophil count, it does not assess eosinophil degranulation or tissue distribution patterns of eosinophilic inflammation in the esophagus, moreover, the EoEHSS has not been correlated with symptomatology. In contrast, EPX degranulation is a validated biomarker that correlates with pediatric dysphagia – even more strongly than eosinophil counts alone(9). While the EPX score did not outperform peak eosinophil counts in terms of diagnostic accuracy in this study, it provides a more comprehensive assessment of eosinophil activity. In summary, quantification of EPX by our EPX scoring system can be used to differentiate children with EoE and PPI-REE relative to GERD and enhance current diagnostic approaches.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Abbreviations:

EoE	Eosinophilic esophagitis
EPX	Eosinophil peroxidase
eos/HPF	Eosinophils per high power field
GERD	Gastroesophageal reflux
H&E	Hematoxylin & Eosin
PPI	Proton pump inhibitor
PPI-REE	Proton pump inhibitor-responsive esophageal eosinophilia

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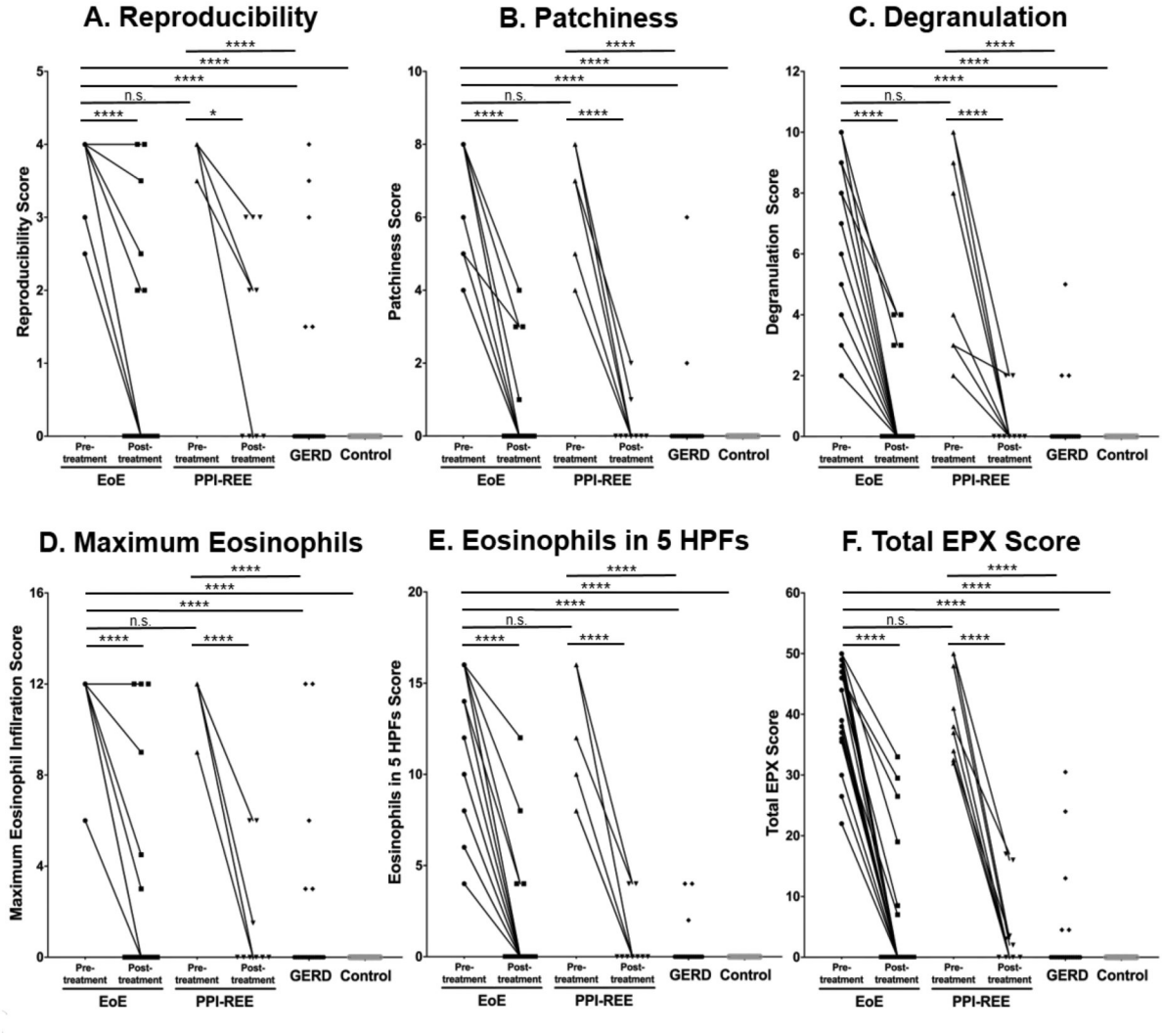

Figure-

Scores for each EPX histology parameter including A) reproducibility (extent of all biopsies with eosinophil infiltration or degranulation), B) patchiness (extent of eosinophil infiltration or degranulation in maximally affected biopsy), C) level of degranulation, D) maximum eosinophils in a single focus, E) average number of eosinophils in five 40X high power fields and F) total EPX Score (EoE n=24, PPI-REE n=9, GERD n=28 and Control n=22, * $P<0.05$, **** $P<0.0001$).

Table-

Demographics, peak eosinophil counts and endoscopic findings of subjects with EoE, PPI-REE, GERD and Control.

	EoE n=24		**PPI-REE n=9**		**GERD n=28**	**Control n=22**
Age Mean years ±SD	3.5±1.8		7.6±5.5		3.7±2.1	12±5.0
Sex n (%)						
Males	20 (83%)		8 (89%)		21 (75%)	9 (41%)
Females	4(17%)		1 (11%)		7 (25%)	13 (59%)
Caucasian	22 (92%)		8 (89%)		23 (82%)	13 (59%)
Atopic Diseases n (%)						
Asthma	10 (42%)		4 (44%)		13 (46%)	0 (0%)
Eczema	12 (50%)		2 (22%)		4(14%)	1 (5%)
Food allergies	11 (46%)		3 (33%)		4(14%)	0 (0%)
Seasonal Allergies	14(58%)		2 (22%)		12 (43%)	0 (0%)
Peak eosinophils	**Pre-treatment**	**Post-treatment**	**Pre-treatment**	**Post-treatment**		
Mean eos/HPF±SD	53.8±31.3	1.5±2.9	53.9±45	1.8±2.9	0.9±2.1	0±0
Endoscopic Findings n (%)	**Pre-treatment**	**Post-treatment**	**Pre-treatment**	**Post-treatment**		
Edema	2 (8%)	0 (0%)	2 (22%)	0 (0%)	0 (0%)	0 (0%)
Rings	1 (4%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Exudate	10 (42%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Furrows	16 (67%)	3 (13%)	5 (56%)	1 (11%)	0 (0%)	0 (0%)
Stricture	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)

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