Eosinophilic Esophagitis in Children

A Pathologic or Clinicopathologic Diagnosis?

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Objective: To determine the accuracy of histopathologic diagnosis in distinguishing eosinophilic esophagitis (EE) from gastroesophageal reflux disease (GERD) in children with upper aerodigestive symptoms.

Design: Masked review of esophageal biopsy findings and comparison with each child’s established clinical diagnosis.

Setting: A tertiary care multidisciplinary aerodigestive center.

Patients: Children were selected from a longitudinal database of all children referred for upper aerodigestive symptoms who underwent a comprehensive evaluation between September 1, 2004, and September 1, 2007. Three groups were recognized based on clinical presentation, initial histologic review, and therapeutic response: children with EE, GERD, or neither.

Intervention: Review of esophageal biopsy findings by a pathologist masked to the child’s clinical or previous pathologic diagnosis.

Main Outcome Measure: Masked histopathologic diagnosis of EE, GERD, or neither.

Results: Medical records from 31 patients were reviewed (11 children with EE, 10 with GERD, and 10 with neither). Diagnostic concurrence between the masked pathologic diagnosis and the established clinicopathologic diagnosis was 64% in children with EE, 70% in children with GERD, and 100% in children with neither. The 4 cases of EE that did not concur were misclassified as GERD when esophageal specimens were evaluated by histopathologic means alone. A clinicopathologic schema for EE developed by gastroenterologists accurately identified 82% of children with EE.

Conclusions: The distinction between EE and GERD cannot be reliably made on histopathologic evidence alone in children with upper aerodigestive symptoms. Despite the recent gastroenterology consensus statement regarding the clinicopathologic diagnosis of EE, children with primary airway symptoms in whom EE is suspected represent a diagnostic dilemma.


Eosinophilic esophagitis (EE) as a clinical entity has become routinely recognized only during the past 10 years. It was first described as a distinct condition in 1993 by Attwood et al in patients with symptomatic dysphagia that was out of proportion to the researchers’ clinical findings on endoscopy. Because the symptoms are primarily dysphagia related, most reports are in the gastroenterology literature. The most common presenting symptoms in children are vomiting, regurgitation, poor eating, and epigastric pain. These symptoms are similar to and difficult to distinguish from those of gastroesophageal reflux disease (GERD). Subsequently, it has been reported that as many as 94% of children with EE exhibit reflux symptoms refractory to proton pump inhibitor (PPI) therapy. During adolescence and entering adulthood, the symptoms manifest as solid food dysphagia and impactions that often require endoscopic removal.

A particular subset of patients has emerged with airway manifestations. The initial report by Orenstein et al described an association between marked eosinophilic esophageal infiltrate and wheezing, congestion, and sinusitis. The first child described in the otolaryngology literature presented after a failed airway reconstruction with stridor, vomiting, and regurgitation. Subsequently, additional children with airway manifestations of EE have been identified.
Distinguishing EE from GERD and establishing a definitive diagnosis of EE remains a challenging clinical problem. In clinical practice, the differentiation between EE and GERD in children with upper aerodigestive symptoms hinges on pathologic examination of esophageal biopsy samples. Such reliance on histopathologic findings raises the question of whether the spectrum of the disease entity is strictly a pathologic diagnosis or a clinicopathologic one.

A clear diagnostic paradigm that defines this entity has yet to emerge. The presenting symptoms are often non-specific, requiring both GERD and other upper aerodigestive disorders to be excluded. There have been a variety of reports describing characteristic endoscopic findings, including concentric rings (trachealization), linear furrows, white exudates, and “crepe paper” appearance. However, none is pathognomonic, and often no gross endoscopic abnormality is seen.9

Endoscopic biopsies are generally performed in multiple locations owing to the known heterogeneity and “patchiness” of the eosinophilic infiltrate.8 There are often no mucosal irregularities. However, when present, biopsy of such sites increases diagnostic yield.7 Some histologic findings, such as basa zone hyperplasia, are common to GERD and EE. Low-grade intraepithelial eosinophilia is commonly seen in GERD.10 Attempts to define specific criteria for EE have led to quantification of eosinophilia, usually by counting the number of eosinophils in the squamous epithelium per microscopic high-power field (HPF). There has been variability in reporting in terms of number of eosinophils and in defining what constitutes an HPF. A variety of reports suggest that patients whose biopsy samples have more than 20 eosinophils per HPF at ×400 magnification represent EE. However, a subset of patients has clinical symptoms that respond to EE therapy and has biopsy samples that contain fewer than 20 eosinophils per HPF. Several different immunoassays and ultrastructural cellular evaluations have yet to add to the routine histopathologic diagnosis of this clinical entity.7,12

The lack of clear diagnostic criteria led to the recent development of a systematic review and consensus statement by the American Gastroenterological Association (AGA).3 The statement is a clear summary of the available evidence regarding EE as a clinical entity, and it provides the following set of diagnostic guidelines: clinical symptoms of esophageal dysfunction, 15 or more eosinophils in 1 HPF, and no evidence of GERD as defined by either lack of response to high-dose PPI therapy or normal pH monitoring of the distal esophagus. The diagnostic picture described relates primarily to the esophageal manifestations of EE.

As our experience with EE has increased, we have found a diagnostic dilemma to exist in children who primarily present with airway symptoms. The general consensus among clinicians is a reliance on histopathologic interpretation for diagnosis. Unfortunately, it is unclear what clinically and histologically constitutes EE in children, especially in those with airway symptoms. The goal of this study is to determine the accuracy of histopathologic diagnosis in distinguishing EE from GERD in children with upper aerodigestive symptoms, particularly those with airway manifestations. In addition, we seek to clarify the potential pitfalls in the diagnosis of EE in these children.

### METHODS

The multidisciplinary pediatric aerodigestive clinic at the Massachusetts Eye and Ear Infirmary is a tertiary care referral center for children with aerodigestive symptoms. A pediatric otorhinolaryngologist, pulmonologist, gastroenterologist, and a speech language pathologist jointly evaluate most children. A longitudinal database is used to track their diagnoses, interventions, and progress.

Institutional review board approval for the study was obtained from the Massachusetts Eye and Ear Infirmary. From the database, children who underwent a comprehensive evaluation, including endoscopy and esophageal biopsy during a 3-year period (September 1, 2004, to September 1, 2007) were identified. Endoscopic examinations consisted of rigid laryngoscopy and bronchoscopy, as well as flexible bronchoscopy and esophagogastroduodenoscopy. Esophageal biopsies consisted of tissue samples obtained from the proximal and distal esophagus under direct visualization using standard techniques during the esophagogastroduodenoscopy portion of each child’s procedure. A total of 273 children underwent similar combined endoscopic procedures for a variety of aerodigestive symptoms.

For this review, the initial diagnosis of EE was defined as upper aerodigestive symptoms in children who satisfied all of the following criteria: (1) minimal or no improvement with antireflux therapy; (2) reported to have eosinophilia on both proximal and distal esophageal biopsy; (3) jointly evaluated, with a pediatric gastroenterologist (S.C.H.) who, after reviewing the pathology report and excluding other systemic and local causes of gastrointestinal eosinophilia, identified and initiated treatment for EE; and (4) demonstrated a documented clinical response to therapy directed at EE.

From the data set, 11 children were identified who met the inclusion criteria. Twenty additional age- and sex-matched children were chosen for whom initial esophageal biopsy findings were consistent with GERD (10 children) or normal (10 children). Medical record review of children with biopsy findings consistent with GERD demonstrated each child to have a reported clinical response to standard antireflux therapies. The medical records of children with biopsy findings interpreted as normal were reviewed and were confirmed to represent children with no overt history or endoscopic findings consistent with EE or GERD. Thus, 3 distinct groups of children were identified as having an initial diagnosis of EE, GERD, or neither.

Subsequently, a board-certified pathologist (J.M.) with expertise in gastrointestinal tract disorders and experience in the pathologic diagnosis of EE reviewed all available esophageal

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**Table 1. Primary Presenting Symptoms in the 31 Study Patients**

<table>
<thead>
<tr>
<th>Group, No.</th>
<th>EE</th>
<th>GERD</th>
<th>Non-EE/GERD</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cough</td>
<td>4</td>
<td>6</td>
<td>5</td>
<td>15</td>
</tr>
<tr>
<td>Dysphagia</td>
<td>2</td>
<td>3</td>
<td>2</td>
<td>7</td>
</tr>
<tr>
<td>Stridor</td>
<td>5</td>
<td>1</td>
<td>1</td>
<td>9</td>
</tr>
</tbody>
</table>

Abbreviations: EE, eosinophilic esophagitis; GERD, gastroesophageal reflux disease.
biopsy findings in a masked manner. Eosinophils were quantified per HPF (×400 magnification), and the highest number obtained was recorded. A pathologic diagnosis of EE, GERD, or neither was assigned based on the number of eosinophils at the proximal and distal biopsy sites. Specimens with 20 or more eosinophils per HPF at each site qualified as EE, those with fewer than 20 eosinophils per HPF were considered GERD, and those with no eosinophils qualified as neither. The masked diagnoses were then compared with the clinical diagnoses and the initial pathology reports.

In addition, the diagnostic guidelines of the AGA (see the introduction to this article) were applied to each patient. Using these guidelines, we arrived at a clinicopathologic diagnosis referred to as the AGA diagnosis. A comparison was then made between the clinical diagnosis and the AGA diagnosis. Ultimately, 3 distinct diagnoses were identified in each of the 11 children initially diagnosed as having EE: (1) a clinical diagnosis as defined by response to therapy, (2) a masked diagnosis based strictly on pathologic review, and (3) an AGA diagnosis based on the clinicopathologic schema developed by gastroenterologists.

**RESULTS**

Thirty-one children (26 boys and 5 girls—a striking male predominance) were included in the study (mean age, 4.6 years). The initial clinical diagnosis was EE in 11 children (9 boys and 2 girls; mean age, 5.3 years), GERD in 10 (7 boys and 3 girls; mean age, 4.0 years), and neither in 10 (all boys; mean age, 4.4 years). Although all of the patients had symptoms of airway compromise, presenting symptoms were simplified to primarily cough, dysphagia, and stridor. The most common symptom was a cough. 

Seven of 11 children (64%) with a clinical diagnosis of EE were also classified as having EE on masked pathologic review. Seven of 10 children (70%) with GERD and all 10 with neither EE nor GERD were similarly assigned by pathologic review. The AGA guidelines identified 9 of 11 children (82%) with a clinical diagnosis of EE who were not identified by the masked pathologic diagnosis were correctly identified as having EE when the AGA guidelines were applied.

The original pathology reports in the EE group were read as diagnostic in 6 of 11 children (55%) and as suggestive of EE in the remaining 5 (45%). Of the 6 initial pathology reports interpreted as diagnostic, 4 were reported as EE on masked pathologic review and 2 were reassigned to GERD, yielding a diagnostic concurrence between initial and blinded pathology reports of 67% (4 of 6).

All initial pathology reports obtained from the GERD subgroup described some degree of epithelial inflammation, including basal cell hyperplasia and variable eosinophilia. All reports mentioned reflux as a possible diagnosis, and none suggested EE or allergic esophagitis as a possible diagnostic consideration. All of the pathology reports in the “neither EE nor GERD” subgroup revealed no diagnostic abnormality and, thus, confirmed the reproducibility of negative pathologic findings in this group. The following cases are representative of the difficulties in diagnosis.

**PATIENT 1**

A 5-year-old girl with a history of prematurity and tracheostomy dependence presented for consideration of decannulation. Her only reported symptoms were tracheostomy capping trial failures, secondary to airway obstruction and stridor. She was being treated for GERD with high-dose PPI therapy. Endoscopic examination demonstrated a posterior glottic scar and associated grade II subglottic stenosis. However, the most striking finding was intense inflammation of her subglottis. Proximal and distal esophageal biopsy findings were reported as “mild EE” without quantification. Radioallergosorbent testing demonstrated reactivity to egg protein. Given the presence of active eosinophilic inflammation in the esophageal biopsy samples despite her current regimen of twice-daily PPI therapy and the absence of other etiologies (no evidence of aspiration on...
modified barium swallow), EE therapy with swallowed fluticasone and egg avoidance was instituted. Follow-up endoscopy 6 weeks later noted marked improvement on endoscopic examination and no inflammation in repeated esophageal biopsy samples (Figure 1B).

Masked review of her biopsy samples resulted in a diagnosis of GERD. In the proximal biopsy sample, 3 eosinophils per HPF were counted, and in the distal biopsy sample, a maximum of 18 eosinophils per HPF were counted, although the distribution in the distal sample was patchy. Given her clinical history and the number of eosinophils per HPF, she would be diagnosed as having EE based on the AGA guidelines.

PATIENT 2

A 3-year-old boy with a history of prematurity presented with long-term daily cough and intermittent stridor, worse at night. He had been diagnosed as having croup 6 times in the past year. His neonatal history was significant because he had been intubated 54 days while in the neonatal intensive care unit. On arrival, he did not have an oxygen requirement. Overall, he was thriving, but his mother reported that he frequently experienced abdominal pain and distention. He underwent high-dose PPI therapy and was scheduled for triple endoscopy. Despite more than 6 weeks of PPI therapy, his abdominal and airway symptoms did not improve. Subsequently, he underwent triple endoscopy that demonstrated no evidence of subglottic stenosis or esophageal abnormalities. A pH probe was nondiagnostic. However, on histologic review, the proximal and distal esophageal biopsy specimens were interpreted as EE. An additional comment by the interpreting pathologist offered a differential diagnosis between reflux and allergy. Results of radioallergosorbent testing were negative to common food allergens. Swallowed fluticasone and montelukast therapy was instituted, with marked improvement in his cough and abdominal symptoms. In the subsequent 2 years, he improved greatly and was weaned off his medications.

On masked review, his biopsy findings were diagnosed as GERD. Quantitative counts demonstrated rare eosinophils and were reported as 10 per HPF distally and 6 per HPF proximally. Based on the number of eosinophils per HPF, he would not be diagnosed as having EE using the AGA guidelines.

The remaining 2 children not identified by histologic criteria demonstrated variable eosinophilia. One child demonstrated dense distal but absent proximal eosinophilia, and the other had mild distal and proximal eosinophilic infiltrate. Both patients presented with primary airway symptoms of cough and stridor, and responded to therapy directed at EE.

COMMENT

In recent years, the clinical entity of EE has been better delineated. The most common clinical presentations are gastrointestinal and are predominantly associated with some degree of dysphagia. However, as awareness of EE has increased, the variability and complexity of the associated symptoms have become further defined. Some patients exhibit extraesophageal manifestations in the upper aerodigestive tract. As described previously herein, a subset of patients present with cough and/or stridor, with some children displaying subglottic narrowing on endoscopy. In addition, the active inflammation of EE
has been suggested to be a cause of failure in airway reconstruction. Thus, a particular concern has been the preoperational evaluation in tracheostomy-dependent children before laryngotracheal reconstruction.

As a tertiary referral center founded on a multidisciplinary approach to pediatric aerodigestive disorders, the Massachusetts Eye and Ear Infirmary has seen a variety of children with upper airway symptoms in the setting of esophagitis. As we have become more proficient at identifying and treating children with EE, we have realized the shortcomings in the literature concerning diagnosis of this entity. As expected, the complexity seems to be most pronounced in children with “atypical” presentations that manifest as noisy breathing or stridor.

This report represents the largest series of patients with airway symptoms associated with EE. Based on the design of the Massachusetts Eye and Ear Infirmary, children are evaluated by a single pediatric otolaryngologist (C.J.H.) and a single pediatric gastroenterologist (S.C.H.), allowing consistency in the evolution of our understanding of EE. Previous reviews in children with airway manifestations of EE are limited to individual case descriptions.

Quantification of eosinophil counts is widely variable in the literature. Most studies address the gastroenterologic symptoms and findings of EE without mention of airway symptoms. As stated previously, 20 eosinophils per HPF is often reported as a suggested quantitative cutoff way symptoms. As stated previously, eosinophils per HPF was associated with failing reflux and promotility therapy in 86% of patients, suggesting a diagnosis other than reflux, such as EE. To our knowledge, no studies specifically address eosinophil counts and correlate association with airway manifestations of EE.

In our experience, there seems to be variable understanding of the role of histopathologic diagnosis in the diagnosis of EE across different medical specialties. These results demonstrate that EE is not solely a histopathologic diagnosis based on quantitative eosinophilia. Children with atypical symptoms and equivocal findings on histologic examination pose the greatest diagnostic challenge. At this time, particularly in children with airway symptoms, EE is a clinicopathologic diagnosis. Although histopathologic diagnosis is a key component in identifying children with EE and accurately identifies most children with the disease, it must be recognized that an appropriate clinical setting supported by endoscopic findings and possibly even response to empirical therapy may be required to establish the diagnosis in select patients. Consideration for empirical therapy may be given for children who have unrelenting clinical symptoms despite traditional therapies and who demonstrate equivocal findings of eosinophilia on esophageal biopsy. Currently, a symptomatic response would be considered an end point, although other histologic markers may provide direction in the future. Duration of therapy in this population remains unclear.

Airway manifestations are rarely reported in EE, and recognition of this unusual presentation of the disease is essential for accurate diagnosis. In this setting, reliance on esophageal biopsy alone, particularly quantitative eosinophil counts, may result in an incorrect diagnosis. Furthermore, the clinicopathologic guidelines developed by gastroenterologists, although an improvement over quantitative histopathologic diagnosis alone, do not accurately diagnose all children with extraesophageal manifestations of EE.

In this series, quantitative eosinophil counts did not recognize 4 of 11 children with EE. This failure was due to eosinophil counts of fewer than the 20 eosinophils per HPF criterion used. Several factors may explain this discrepancy. Contributing factors likely include a combination of sampling error related to the known heterogeneity of the eosinophilic infiltrate in EE and the spectrum of disease in this population, particularly those with airway symptoms.

An interesting finding in this population is the male predominance. A 75% to 80% male predominance has been described in EE, thus echoing our experience. Overall, there is a slight male predominance in the number of children seen by our aerodigestive diagnostic center as a whole. Although EE clearly affects males more frequently than females, it is unclear whether the natural male bias of the Massachusetts Eye and Ear Infirmary and the somewhat limited sample size contribute to the finding.

The described patients serve as complex examples of cases when the diagnosis of EE rests on a combination of clinical and histologic findings. As demonstrated, many children were referred with primary airway symptoms and, although the initial pathology reports raised a suspicion of EE, quantitative eosinophil counts were equivocally low. Most significant is the dramatic improvement that each child experienced on the institution of therapy directed at EE.

Several weaknesses are inherent to this study. Particularly, the retrospective design limits the conclusions that can be drawn. In addition, this article represents an initial review; thus, we are limited in the amount of patient data available. Every effort to standardize identification of patients was made, but the specific difficulty that drove this study was the evolving definition of EE.

Future efforts are necessary to more clearly define the spectrum of EE. Further correlations with multiple clinical and histologic factors are under way to further define EE, particularly in children with atypical presentations. In addition, the identification of specific histopathologic markers to improve the diagnostic specificity would contribute greatly to the diagnostic algorithm. Ultimately, as EE becomes further defined, prospective designs can be used to track outcomes.

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Hartnick. Analysis and interpretation of data: Brigger, Misdraji, and Hardy. Drafting of the manuscript: Brigger. Critical revision of the manuscript for important intellectual content: Brigger, Misdraji, Hardy, and Hartnick. Administrative, technical, and material support: Brigger and Misdraji. Study supervision: Hardy and Hartnick.

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REFERENCES