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The otolaryngologic manifestations in children with eosinophilic esophagitis[☆]

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ABSTRACT

Objectives: (1) To describe the incidence of eosinophilic esophagitis (EoE) in the population of patients undergoing esophagoscopy with biopsy by a pediatric otolaryngology service. (2) To elucidate the demographics, presenting symptoms, and endoscopic findings in children with EoE.

Design: Case series.

Patients/methods: The reports of esophageal biopsy specimens taken over 5 years in 2429 patients were reviewed. Ninety-two patients who received their initial diagnosis of EoE by the pediatric otolaryngology service with specimens showing 15 or greater eosinophils per high power field (HPF) were included. **Interventions:** The demographic data, history, presenting symptoms, and endoscopic findings were reviewed retrospectively for the patients.

Main outcome measure: The percentage of children diagnosed with EoE of all children undergoing esophageal biopsy.

Results: A total of 92 children were diagnosed with EoE (3.8% of total children biopsied). The mean age at biopsy was 4.4 years, much lower than previously reported in the literature (approximately 8 years); 73% were boys and 27% girls. The main presenting symptom was cough (46%) followed by hoarseness, throat clearing, burping/vomiting, and abdominal pain. Forty three percent had a history of asthma and 17% a history of GERD. Half of patients had esophageal edema, a third were normal, and only a quarter had mucosal furrowing on endoscopic examination.

Conclusions: EoE is increasingly diagnosed as a clinical entity with a distinct symptom profile and etiology. Increased understanding of EoE and its predisposing factors requires a multidisciplinary approach to diagnosis and management involving the pediatric otolaryngologist.

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1. Background

While well known in the field of gastroenterology, eosinophilic esophagitis (EoE) is a relatively new diagnosis in the pediatric otolaryngology practice. A search of the Pubmed database for “eosinophilic esophagitis” yielded only 14 articles in the otolaryngology literature, six of those in the past year. As a result, the incidence and presenting symptoms in the pediatric otolaryngology population is still being elucidated. EoE classically presents with food impaction, vomiting or dysphagia, with symptoms similar to GERD. In 2000, Orenstein et al. first described the association of EoE and respiratory disease in a group of patients

presenting through the gastroenterology clinic, concluding that 62% of the children had a history of chronic respiratory disease including asthma, aspiration pneumonias, and recurrent respiratory illnesses [1]. Eosinophilic esophagitis first appeared in the otolaryngology literature as a case report in 2002 describing a pediatric patient who had subglottic stenosis and allergic esophagitis [2]. Subsequent research expanded on the spectrum of related otolaryngology symptoms including rhinosinusitis, Eustachian tube dysfunction, sleep disordered breathing, airway stenosis, cough, choking, hoarseness and globus sensation [3,6]. Additional work elucidating the significant airway endoscopic findings in children with EoE noted subglottic stenosis, laryngeal edema and effacement of the ventricles that corresponded with the severity of airway symptoms [4,5,7]. These case studies and series have shown the impact of this disease on the entire upper aerodigestive tract not just the esophagus. Bove et al. biopsied the pharynxes of several patients with biopsy proven EoE and found uniformly that there was no eosinophilia in the adjacent mucosa of the pharynx [8].

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An increasing number of patients who underwent esophagoscopy with biopsy for a variety of reasons whose biopsy demonstrated eosinophilic esophagitis (EoE) was noted at our institution. These patients represented a much more heterogeneous population of patients and their symptom profile was distinct when compared with typical patients with EoE described in the gastroenterology literature. These included upper airway symptoms including hoarseness or cough rather than food impaction or abdominal complaints. There is a relative paucity of data on this topic in the otolaryngology literature to address management issues. The goal of our study was to review our population of pediatric patients who were diagnosed with EoE primarily by a pediatric otolaryngologist to describe the incidence, demographics, presenting symptoms and esophagoscopy findings.

2. Methods

All patients from birth to age 18 years who underwent rigid esophagoscopy with biopsy by the pediatric otolaryngology service for any reason from January 2001 to December 2005 were identified using a computerized medical record search of Current Procedure Terminology code 43202. Esophagoscopy was almost always performed in conjunction with flexible fiberoptic laryngoscopy, direct laryngoscopy, and bronchoscopy. None of the procedures in the current study were undertaken to manage an acute esophageal impaction. Two biopsies were taken; one from the distal esophagus and one from the proximal esophagus. All biopsy specimens were reviewed by one of the surgical pathologists at Children's Hospital of Pittsburgh. Esophageal specimens underwent routine processing with serial sectioning and staining with hematoxylin–eosin. The number of eosinophils per high power field (HPF) was reported as well as other characteristics of inflammation including proliferative changes to the basal layer, spongiosis, and elongated papillae. Most of the final diagnoses were “eosinophilic esophagitis” but there were some biopsies where the diagnosis was “esophagitis” but the microscopic description included the number of eosinophils per HPF as greater than 15; therefore they were included in the review. The decision to use 15 eosinophils per HPF was determined by a review of the literature [9–12] and after consulting with the pediatric gastroenterology co-author (AG). The pathology reports for each patient who underwent esophageal biopsy were reviewed. The medical record of any patient who had a biopsy with greater than 15 eosinophils per HPF was reviewed, including clinic records, patient history questionnaires, operative reports including endoscopic findings and photographs, pathology reports, and follow-up with pediatric otolaryngology and with any referring consultants. Patient data collected from those charts where biopsies showed greater than 15 eosinophils per HPF included: age, sex, date of biopsy, duration of symptoms, symptom profile (including GI pain, throat clearing, cough, hoarseness, burping, vomiting), relevant past history including history of croup, asthma, allergic rhinitis, as well as tracheostomy dependence and subglottic stenosis. Any history and blood or skin test results of food or environmental allergies were also recorded. Operative endoscopic findings were recorded, including: active reflux, mucosal friability, posterior glottic edema or erythema, and mucosal furrowing. The number of eosinophils per HPF was reported and the patients with greater than 15 eosinophils per HPF were included. Patients with greater than 15 eosinophils per HPF were started on a proton pump inhibitor (PPI) and sent for consultation with a pediatric gastroenterologist who would then perform esophagoscopy with biopsy to assess if the eosinophilia persisted and if a diagnosis of EoE could be given, or if the eosinophilia was due to GERD and resolved with PPI treatment. Often, airway endoscopy was performed in conjunction with the esophagoscopy.

This study was approved by the University of Pittsburgh institutional review board and was designated as “exempt” under section 45 Code of Federal Regulations 46.101b.

3. Results

A total of 2429 patients undergoing 2861 biopsies performed by the pediatric otolaryngology service were reviewed. The patients were from the same referral area encompassing western Pennsylvania. There was not a significant difference in the number of patients diagnosed with EoE each year as the study progressed over its five years. Ninety-two patients with 15 eosinophils per HPF or greater (Fig. 1) were identified. The mean age at the time of the initial biopsy was 4.4 years. Twenty-five of the patients were girls (27%) and 67 were boys (73%). Symptoms at the time of presentation (Table 1) were most commonly: cough (46%) and hoarseness (38%) (with similar percentages when analyzed by gender). Other symptoms in decreasing order of frequency were: burping (31%) and throat clearing (30%).

Approximately half of patients had a history of asthma (Table 2). A significant number of patients had family history of allergic rhinitis or environmental allergy. The findings at the time of esophageal endoscopy showed that approximately half of the patients had esophageal edema (Table 3). Approximately 30% of the endoscopic examinations were normal. Fig. 2 depicts mucosal furrowing with whitish exudates which were also a feature documented on endoscopy in a percentage of patients.

The aims of the study were to determine the prevalence of EoE in patients who underwent esophagoscopy with biopsy as well as compare patient demographics and symptom presentation to patients described in the gastroenterology literature. An additional aim was to determine the symptoms, relevant history, and endoscopic findings in children who are both tracheotomized (especially those with subglottic stenosis) and have EoE in order to eventually elucidate reasons for airway findings in children with EoE, especially why laryngotracheal reconstruction (LTR) may fail in this unique subpopulation of children with EoE and airway stenosis (Tables 4 and 5).

One of the more interesting findings is that 13 (14%) of the patients had a tracheostomy tube in place and 9 (10%) of all 92 patients had endoscopic findings documenting subglottic stenosis. This was almost exclusively a phenomenon of individuals with a greater number of eosinophils per HPF. The average number of eosinophils per HPF in these patients was 31 compared to 26 for the remainder of

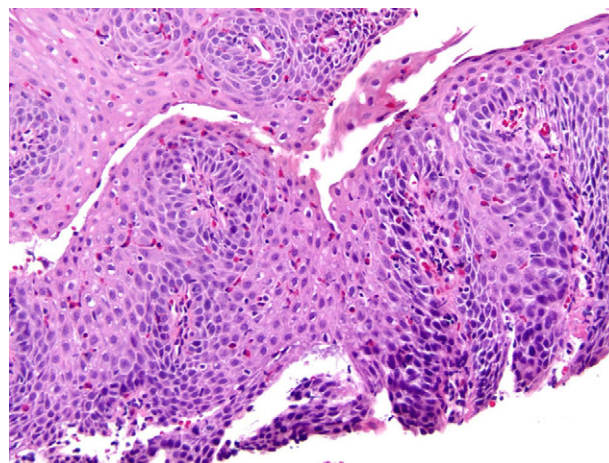


Fig. 1. Esophageal biopsy from a child with diagnosis of EoE; this child has greater than 20 eosinophils in this high power field. Hematoxylin and eosin stain, 400× magnification.

Table 1

Prevalence of symptoms in children diagnosed with eosinophilic esophagitis (EoE) in a pediatric otolaryngology clinic. Obtained from intake questionnaire completed by patients' parents.

Presenting symptom	Symptom prevalence
Cough	46%
Hoarseness	38%
Burping	31%
Throat clearing	30%
Vomiting	28%
Abdominal pain	16%

Table 2

Prevalence of elements of past medical history in children diagnosed with EoE in a pediatric otolaryngology clinic. Obtained from intake questionnaire completed by patients' parents.

Element of past medical history	Prevalence of past medical history
Environmental allergies	71%
Asthma	43%
Food allergies	40% ^a
Allergic rhinitis	28%
Recurrent croup	21%

^a Of all patients; percentage of patients with food allergies who were tested for food allergies by skin prick testing = 78%.

Table 3

Prevalence of specific endoscopic findings in children at the time of their diagnosis with EoE. Obtained from operative report descriptions and/or operative endoscopic photographs.

Endoscopic findings	Prevalence of endoscopic findings
Mucosal edema	53%
Furrowing	29%
Mucosal erythema	21%
Friability	14%
Active reflux	6%
Normal	30%



Fig. 2. Endoscopic photograph of a child with EoE noting mucosal furrowing with white exudates.

Table 4

Prevalence of abnormal airway findings in children diagnosed with EoE. Obtained from clinic notes and operative reports.

Airway findings	Prevalence of airway findings
Subglottic stenosis	10%
History of tracheostomy	14%

Table 5

Percentage of children with specific treatment or follow-up initiated in a pediatric otolaryngology clinic. Obtained from clinic notes.

Follow-up and treatment	Percentage of patients with specific treatment
G1 referral	64%
H2 blockade	59%
PPI	39%
Topical steroid	30%
Dietary changes	22%

the patient cohort. There seems to be a correlation between the severity of the EoE and the persistence/progression of subglottic stenosis although this could not be fully quantified in this study.

4. Discussion

Eosinophilic esophagitis was defined by Atwood in 1993 in a group of patients who had dysphagia, normal pH probes and a high number of eosinophils on esophageal biopsy [13]. EoE is suspected when patients do not respond to standard reflux treatment and have normal pH probes [5,14–17]. While these patients usually present to a gastroenterologist with dysphagia, nausea/vomiting, epigastric pain, food impaction or strictures, it is now recognized that EoE causes a myriad of symptoms involving the entire upper aerodigestive tract [1–5,15–17]. It is vital to recognize the airway manifestations of this disease and be able to distinguish it from GERD. In our study, all 92 patients received their diagnosis of EoE from the pediatric otolaryngology team. Once the diagnosis of EoE was established, the patients were started on a PPI and the gastroenterology team was consulted. After six to eight weeks of treatment with the PPI, they returned to the operating room for an esophagogastroduodenoscopy (EGD) with biopsies, often as a combined procedure with the pediatric otolaryngology team performing an airway endoscopy.

The diagnosis of EoE was made in approximately 4% of the 2429 patients who underwent esophageal biopsy over 5 years. This study retrospectively reviewed 92 pediatric patients presenting to pediatric otolaryngology with a variety of upper aerodigestive tract complaints who were diagnosed with EoE. All of the 92 patients in the study demonstrating greater than 15 eosinophils per HPF were initially seen and diagnosed by a pediatric otolaryngologist. The most common complaint was cough in 54%, followed by hoarseness (38%), throat clearing (30%), burping/vomiting (31%) and abdominal pain (16%). The average age at diagnosis was 4.4 years and males (73%) were more often affected than females (27%). The mean age of presentation in most studies is approximately 10 years old [1,3,15,16]. Males are more commonly affected at 65–81% [1,3,15–17]. Concomitant diseases included asthma (43%), allergic rhinitis (28%) and a history of croup (22%). On endoscopy, half of the patients had esophageal edema, less than a third were considered normal and just over one quarter had mucosal furrowing. Nine patients had subglottic stenosis and thirteen patients had tracheotomy tubes in place at the time of endoscopy.

Of great interest is the patient group with airway findings. A significant number of tracheostomy patients, especially those tracheotomized for subglottic stenosis, whose interval endoscopy and biopsy findings showed EoE were unexpectedly noted during

the data collection and analysis. This issue became more practical instead of merely academic when a tracheotomized patient with subglottic stenosis and with EoE who succeeded after laryngo-tracheal reconstruction (LTR) in the short term eventually failed with acute airway obstruction and restenosis requiring repeat tracheotomy. The concern was that the effect of the EoE on the remainder of the upper aerodigestive tract may have contributed in some way to the LTR failure.

The diagnosis of EoE is a clinicopathologic one with the mucosal biopsy aiding in the establishment of the diagnosis. The biopsy result is based on the number of eosinophils per HPF in the superficial layer of the esophageal epithelium. Different authors have specified varying numbers of eosinophils to qualify for diagnosis with greater than 20 generally agreed upon and 7–20 under dispute [4,5,13–17]. The latest consensus recommendations published by Liacouras et al. confirm 15 eosinophils per HPF as the minimal standard for the diagnosis of EoE [9]. Eosinophils on esophageal biopsy may also be associated with GERD but are usually less than seven in number [18].

The gross esophageal appearance of eosinophilic esophagitis on endoscopy is inconsistent. Characteristic findings if seen on endoscopy include white exudate, “crepe paper” tissue, concentric rings (so-called trachealization of the esophagus), linear furrows and strictures [1,3,5,15–17]. However, 20–32% of patients were noted to have a “normal” appearing esophagus [3,16]. This correlated with our endoscopic findings which were normal in 30% of patients. Findings on endoscopy typically do not correlate with the number of eosinophils identified pathologically. Also, the effect of the disease on the esophagus is not homogenous so three levels of biopsy are recommended.

The pathophysiology of EoE is not well understood. Food, aeroallergens and fungi are known to cause an eosinophilic response. With reports of up to 70% of patients having atopic disease and some patients with increased peripheral eosinophils and IgE levels, the role of food and environmental allergy is being further studied [1,3,5,15,17]. In some studies, 50–60% of patients tested positive for food allergies [1,3,15,16]. A case report describes exacerbations of EoE during pollen season [19]. Of note, asthma has been reported as a concomitant disease in 24–40% of patients with EoE [1,3,15]. The mouse model for eosinophilic disease requires either repeat respiratory antigen exposure or cutaneous exposure prior to a single respiratory exposure in order to induce EoE [20,21].

Treatment for EoE currently consists of swallowing topical corticosteroids or food elimination diet with some patients requiring an elemental diet. Debate exists over which treatment modality is most appropriate [1,3–5,16,17]. Factors affecting treatment include compliance, length of treatment and side effects such as thrush. Newer treatments include therapy with anti IL-5 (mepolizumab) [22].

The retrospective nature of the study introduces an inevitable limitation. The patient data collected from the parent questionnaire depend necessarily on the memory of the individual completing the questionnaire and the inherently subjective nature of the symptom profile. Because patients with tracheostomies undergo panendoscopy at regular intervals, there may be a selection bias introduced in patients with EoE and a tracheostomy since they undergo relatively frequent esophageal biopsies. An additional limitation is introduced by the nature of the diagnostic criteria for EoE. There is debate about the specific histopathologic diagnostic criteria in a more clinical setting.

5. Conclusion

It is important to understand and recognize this disease, as the otolaryngologist may be the first clinician to see these patients and diagnose EoE. However, given the multiple potential contributing

factors and affected sites of the upper aerodigestive tract, these patients should be treated through a multidisciplinary approach. Further studies are being pursued to better characterize the presentation, understand the pathophysiology and determine the most appropriate treatment for EoE.

Conflict of interest statement

All authors have no financial and personal relationships with other people or organizations that could inappropriately influence or bias their work to disclose.

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