Eosinophilic Esophagitis

A Retrospective Review of Esophageal Biopsy Specimens From 1992 to 2004 at an Adult Academic Medical Center

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Abstract

Eosinophilic esophagitis (EE), initially described in children, is now recognized in adults. The prevalence of EE in adults is largely unknown. Our goals were to determine the prevalence of EE in an adult population undergoing esophagogastroduodenoscopy with biopsy as originally reported and on retrospective review, the rate at which EE was present before this diagnosis was readily appreciated, and whether the prevalence of EE has changed over time.

We reviewed esophageal biopsy specimens from 1992 to 2004. If there were more than 15 eosinophils per high-power field and confirmatory clinical information was available, EE was diagnosed. The initial (prereview) prevalence was 1.3%; prevalence on retrospective review was 1.7%. Prevalence was higher in later years (3.8%) compared with early years (0.3%).

The demographics of our patients with EE are generally similar to what has been reported. Our results suggest the prevalence of EE is increasing and that pathologists provide accurate diagnoses in the face of changing criteria and significance.

Eosinophilic esophagitis (EE) was defined by a recent consensus recommendation from the American Gastroenterological Association Institute and North American Society of Pediatric Gastroenterology, Hepatology and Nutrition as "a primary clinicopathologic disorder of the esophagus, characterized by esophageal and/or upper gastrointestinal tract symptoms in association with esophageal mucosal biopsy specimens containing ≥15 intraepithelial eosinophils/HPF [high-power field] in 1 or more biopsy specimens and absence of pathologic gastrointestinal reflux disease as evidenced by a normal pH monitoring study of the distal esophagus or lack of response to high dose proton pump inhibitor medication."[1] Although it was first described in 1977,[2] it was only in the mid 1990s after reports by Attwood et al[3] in 1993 and Kelly et al[4] in 1995 that EE became more recognized by gastroenterologists and pathologists. Since that time, the number of articles published annually about EE has continued to increase.

Because it was initially described in children, characterization of EE among adults has lagged. We know that EE has distinct clinical and endoscopic findings. Clinical symptoms include dysphagia, particularly to solids, sometimes associated with food impaction, and resistance to reflux therapy. Endoscopic findings include rings, furrows, white specks, and small-caliber esophagus.[5-11] In children and adults, EE is more common in males. In the United States, EE is found in all regions without confinement to a particular geographic area or latitude.[12]

Although eosinophils can normally be found elsewhere in the gastrointestinal (GI) tract (stomach, small and large intestine), they are not typically found in the esophagus.[13] Eosinophils in the GI tract likely protect against infection,

especially through IgE-mediated immune reactions. Similar to what is seen in other parts of the body, eosinophils can be seen in the GI tract in malignancy, infection, collagen vascular disease, drug reaction, inflammatory bowel disease, and hypereosinophilic syndrome. Once those causes of eosinophilia have been excluded, the presence of eosinophilia in the esophagus is associated with gastroesophageal reflux disease, eosinophilic gastroenteritis (EGE), and EE.[1] Gastroesophageal reflux disease is typically characterized by heartburn and/or regurgitation clinically and increased esophageal acid exposure shown by intraesophageal pH monitoring. Endoscopy may reveal erythema, edema, and/or linear ulcers in the distal esophagus, and histologic examination may show low-level (<7/HPF) eosinophilic infiltration of the esophageal squamous epithelium, basal cell hyperplasia, and elongated lamina propria papillae.[8] EGE is also a clinicopathologic entity, characterized by GI symptoms, eosinophilic infiltration of the GI tract, or radiologic findings (prominent folds) with peripheral blood eosinophilia and an absence of parasitic and extraintestinal disease.[14] Patients with EGE typically complain of abdominal pain, nausea, weight loss, and/or diarrhea. Because the findings are isolated to the esophagus, EE is considered distinct from EGE.[15] Typical findings of EE were described in the preceding paragraphs.

In EE, eosinophils are accompanied by other inflammatory cells, including T lymphocytes, dendritic cells, and mast cells.[13] Esophageal eosinophils are activated and degranulated in a subset of patients with EE.[16] This finding is significant because it implicates eosinophils not only as a marker of EE, but also as part of the pathophysiology as the eosinophil granules contain proteins that mediate tissue injury. In fact, esophageal fibrosis correlates with the extent of eosinophil activation rather than the number of intraepithelial eosinophils.[16] One of the primary recruiters of eosinophils to the esophagus is thought to be eotaxin. Eotaxin has been shown to be the most highly induced gene in the esophagus of children with EE.[17] Interleukin 5 may also have a role in recruitment of eosinophils to the esophagus in EE because the number of esophageal eosinophils decreased after administration of an antibody to interleukin 5.[18]

The annual incidence of EE in the general population of Olten County, Switzerland, was estimated by Straumann and Simon[11] to be 1.7/100,000 (range, 0-8). They also suggested an increasing prevalence: 2:100,000 in 1989 to 27:100,000 in 2004. Kapel et al[12] also showed an increasing prevalence in the United States from 0.1% in 2002 to 1.9% in 2005. On the other hand, investigators from the University of Iowa reported a stable incidence of EE in 1990 vs 2005.[19]

The current study consists of a retrospective review of esophageal biopsy specimens at an adult academic medical center. The goals of this study were to determine the prevalence of EE in an adult population undergoing esophagogastroduodenoscopy with biopsy of the esophagus as originally reported and on retrospective review, the rate at which EE was present before this diagnosis was readily appreciated, and whether the prevalence of EE has changed over time.

We initially hypothesized that the prevalence of EE would be stable over time but that because of the recent increased awareness of EE, pathologists would be more likely to correctly make a diagnosis of EE in the present decade as compared with the previous, and, therefore, on retrospective review and application of today's "standards," more cases of EE were present in the 1990s than previously appreciated.

Materials and Methods

The surgical pathology database at the University of Pennsylvania Medical Center, Philadelphia, was queried for esophageal biopsies performed in the months of May and June between 1992 and 2004 (a convenience sample selected in allergy season to identify as many cases as possible). Cases that were part of a resection and cases that originated elsewhere were excluded. Each biopsy specimen was reviewed by 1 of 4 pathologists. The number of intraepithelial eosinophils in each HPF (40× objective; total magnification, ×400) was counted. The peak eosinophil count (highest number of eosinophils per HPF) was determined for each biopsy specimen. Cases with 1 or more HPF with 15 or more eosinophils were considered possible cases of EE, and clinical information was obtained, when available. Cases with neoplasia, acute inflammation, or ulceration were not considered diagnostic of EE.

Results

During May and June between 1992 and 2004, 606 esophageal biopsies were performed; the number of biopsies increased in the last half of the study. Of the 606 cases, 584 were available for review, including at least 92% each year **Figure 1**. Initially, 8 of 606 biopsy specimens had been

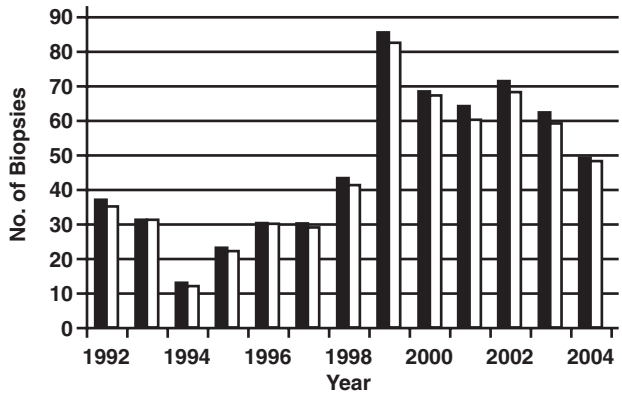

Figure 1 Total number of esophageal biopsy specimens (black bars) and the number available for review (white bars).

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reported as EE (prevalence, 1.3%). On retrospective review, 17 (of 584) biopsy specimens had 15 or more eosinophils per HPF; clinical information was available for 13 (76%) of 17 cases. Of the 13 cases with available clinical information, 10 had clinical and/or endoscopic findings consistent with EE (prevalence, 1.7%); these are considered confirmed cases of EE. One of the initially reported EE cases was not available for review **Figure 2** and **Table 1**.

Among the 10 patients with confirmed EE, the M/F ratio was 7:3. Patients ranged in age from 19 to 64 years (mean, 33.4 years; median, 30 years). The average maximum (peak) number of eosinophils per HPF was 43.5. Women had an average peak eosinophil count of 44.7/HPF. Men had an average peak eosinophil count of 43/HPF.

Of the 10 confirmed cases of EE identified on retrospective review, 7 were initially reported as EE. The other 3 cases were initially reported as florid esophagitis, reflux, or normal.

Initially, a diagnosis of EE was not reported until 2001. On retrospective review, 1 confirmed case was identified before that year (original diagnosis, florid esophagitis). Between 2001 and 2004, 9 confirmed cases of EE were identified retrospectively, 2 of which were initially reported in a different way (reflux or normal). These findings are summarized in **Table 2**. By χ^2, this difference was not significantly different ($P = .2$).

As previously stated, among the confirmed cases, one was identified between 1992 and 2000 (prevalence, 0.3%), and the remaining 9 cases were identified between 2001 and 2004 (prevalence, 3.8%). This difference in prevalence was statistically significantly different by χ^2 analysis ($P \leq .01$) **Table 3**.

Discussion

This study is significant because it demonstrates an increasing prevalence of EE; that pathologists continue to provide accurate diagnoses, even in the face of changing criteria and significance; and that our EE population is similar to others with respect to demographic and histologic factors.

This study demonstrates that among patients who undergo biopsy during esophagogastroduodenoscopy, historically, at least 1.7% of them have EE. The results of this study suggest that the prevalence is increasing, up to 3.8% of patients undergoing biopsy during esophagogastroduodenoscopy in the last 4 years of our study compared with 0.3% in the first 9 years. This apparent increase in prevalence can be accounted for by several mechanisms: (1) As a disease with stable incidence with little morbidity, the population of EE will rise as new cases are diagnosed in addition to a surviving population of previously diagnosed patients. (2) As gastroenterologists became more aware of EE over time, they may have been more likely to perform endoscopy on symptomatic patients, more likely to identify the sometimes subtle findings of EE, and more likely to biopsy patients

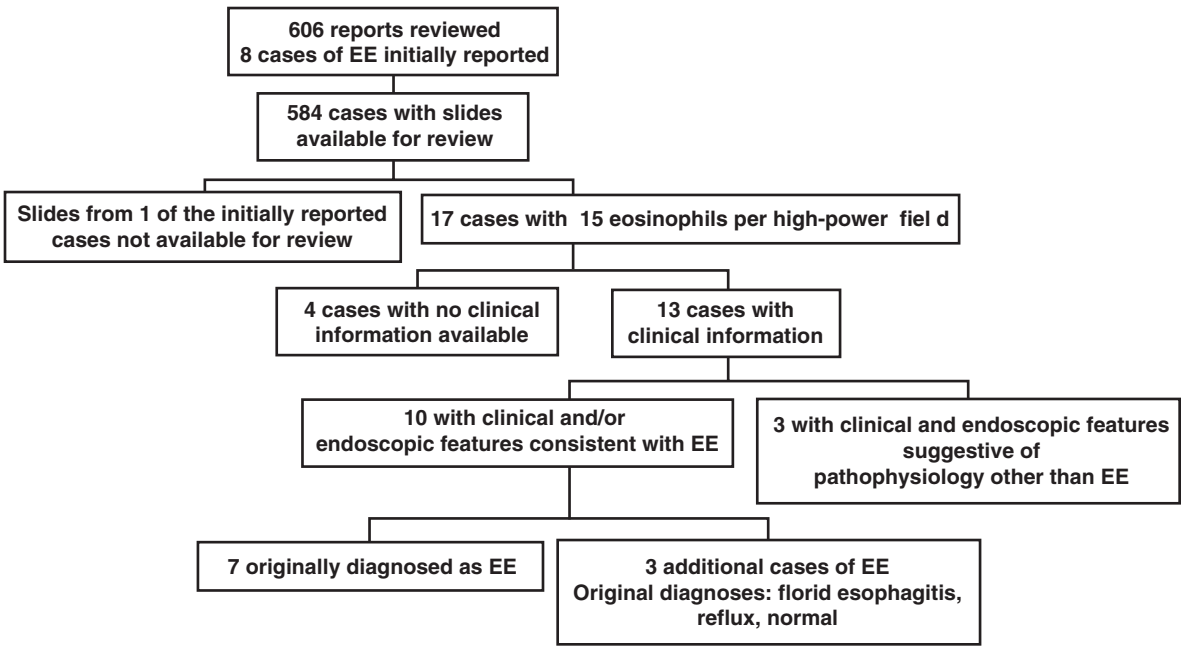

Figure 2 Retrospective case review breakdown. EE, eosinophilic esophagitis.

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Table 1
Clinicopathologic Data for Patients With 15 or More Eosinophils per High-Power Field

Year	Clinical History	Sex/Age (y)	Original Pathologic Diagnosis
	Confirmed EE Cases		
2001	Reflux esophagitis	M/64	Eosinophilic inflammation
2002	Clinical and endoscopic findings compatible with EE; positive allergy testing and response to steroids	M/19	EE
2002	Clinical and endoscopic findings compatible with EE; positive allergy testing and response to steroids	M/19	EE
2002	Clinical and endoscopic findings compatible with EE; positive allergy testing and response to steroids	M/19	EE
2003	Clinical and endoscopic findings compatible with EE; positive allergy testing and response to steroids	M/32	EE
2003	Clinical and endoscopic findings compatible with EE; positive allergy testing and response to steroids	F/28	EE
2004	Clinical and endoscopic findings compatible with EE; positive allergy testing and response to steroids	M/56	EE
1992	Dysphagia	M/36	Florid esophagitis
2003	Endoscopic findings compatible with EE	F/23	Reflux esophagitis
2003	Dysphagia	F/38	No specific pathologic change
	Clinical Information Unavailable		
1992	Unavailable	F/46	Reflux esophagitis
1995	Unavailable	M/37	Reflux esophagitis
1996	Unavailable	F/39	GERD
2000	Unavailable	F/69	Acute esophagitis
	Clinical Information Suggestive of Pathophysiology Other Than EE		
2000	Heartburn; normal endoscopy	F/25	Reflux esophagitis
2002	*Candida* esophagitis	F/32	Acute esophagitis
2003	Barrett esophagus	M/57	Reflux esophagitis
	Original Slides Not Available for Review		
2003	Not available		EE

EE, eosinophilic esophagitis; GERD, gastroesophageal reflux disease.

Table 2
Initial vs Retrospective Diagnosis of EE

	1992-2000	2001-2004	Total
EE cases reported initially	0	7	7 (excludes the case not available for retrospective review)
EE cases on retrospective review	1	9	10
Additional EE cases identified	1	2	3
No. of esophageal biopsies	349	235	584

EE, eosinophilic esophagitis.

with subtle or no endoscopic changes but with other factors consistent with EE. Similarly, awareness among pathologists will also increase the recognition and diagnosis of EE. (3) The incidence of EE, like other atopic disorders, is on the rise.[20] (4) Patients not satisfactorily diagnosed and treated will tend to come back over time until the correct diagnosis is made by virtue of advancement in our understanding of these diseases and in the face of continuing symptoms that have not been effectively treated. (5) Artifact that was secondary to lack of clinical information disproportionately affecting earlier years of the study.

We hypothesized that more cases of EE were misdiagnosed in the 1990s compared with the 2000s; this study provides evidence against this theory. In this sample, a case of EE was not reported before 2001. On retrospective review, 1 case was identified in that time. Between 2001 and 2004, 7 cases were initially reported, with 2 additional cases identified on retrospective review. However, as one might expect, several of the cases without clinical information available were from the initial part of the study; specifically, the 4 cases with 15 or more eosinophils per HPF and no clinical information available were from 1992, 1995, 1996, and 2000. If clinical

Table 3
Prevalence in Early vs Later Years

	1992-2000	2001-2004
EE cases	1	9
Total biopsies reviewed	349	235
Prevalence (%)	0.3	3.8

EE, eosinophilic esophagitis.

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information had been available to support a diagnosis of EE in these cases, our hypothesis would have been correct—more cases of EE were missed in the 1990s than in the 2000s.

The demographics of our patients with EE are generally similar to what has been reported by others. Although there is a perception that EE is a disease of children and young adults, our data, like those of others, confirm that EE can affect people of any age.

Conclusion

EE is not uncommon among patients undergoing esophagogastroduodenoscopy with biopsy of the esophagus, with a prevalence of at least 1.7% in our population. Evidence that the prevalence of EE is increasing is provided, although whether this is a true increase in the disease or a result of increased recognition factors is difficult to determine. Pathologists at this institution were not more likely to diagnose EE correctly in the present decade when compared with the 1990s.

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