

Low Grade Esophageal Eosinophilia in Adults: An Unrecognized Part of the Spectrum of Eosinophilic Esophagitis?

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Abstract

Background Eosinophilic esophagitis (EoE) is defined by a minimum of 15 eosinophils (eos) per high-powered field (HPF) on esophageal biopsy, along with esophageal symptoms and the exclusion of gastroesophageal reflux (GERD). The clinical significance of fewer eosinophils is unknown.

Methods Fifty-nine adult patients without a previous diagnosis of EoE with esophageal biopsies containing 1–14 eos per HPF (low grade eosinophilia) and 418 adult patients with ≥ 15 eos per HPF were identified by retrospective review. Patients were divided into group A (1–9 eos per HPF), group B (10–14 eos per HPF), and group C (≥ 15 eos per HPF) with a chart review of clinical and demographic data.

Results While dysphagia and atopy (asthma and allergic rhinitis) were more common in patients with ≥ 15 eos per HPF (group C) than those with low grade esophageal eosinophilia (groups A and B) (93 vs. 88%, $P = 0.02$), food impaction and heartburn occurred at an equal frequency across all patient groups. Endoscopic findings were likewise similar between groups. Of the 14 patients with

low grade esophageal eosinophilia who underwent repeat endoscopy a mean interval of 42 weeks (range 8–118 weeks) later, five (36%) met conventional diagnostic criteria for EoE of 15 or greater eos per HPF. Follow-up in ten patients treated with topical corticosteroids noted improvement in nine, with mean follow-up of 8 weeks (range 4–12 weeks).

Conclusion Some adult patients with dysphagia and less than 15 eos per HPF have similar endoscopic findings and clinical course to patients meeting the consensus definition of EoE. Further evaluation of patients with low grade esophageal eosinophilia is needed.

Keywords Eosinophilic esophagitis · Eosinophils · Esophageal eosinophils · Low grade eosinophilia

Introduction

Eosinophilic esophagitis (EoE) was first described by Landres et al. [1] in 1978. Initially believed to be a rare condition, the diagnosis of EoE has dramatically increased in recent years [2, 3]. This increase has largely been attributed to increased recognition [4]. However, there is some evidence for a true increase in incidence [5–7].

Eosinophilic esophagitis is characterized by eosinophils in the squamous epithelium or deeper layers of the esophagus. Eosinophils are normally absent from the esophagus, but are seen in conditions other than EoE, including gastroesophageal reflux, collagen vascular diseases, Crohn's disease, infections, and achalasia [6–8]. However, mild esophageal eosinophilic infiltration, defined by 1–14 eosinophils (eos) per high-powered field (HPF) on esophageal biopsy specimens, is historically considered representative of gastroesophageal reflux disease (GERD)

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rather than eosinophilic esophagitis [9, 10]. Moreover, greater than 20 eos per HPF has traditionally been accepted as diagnostic of EoE [2, 4, 8, 9, 11–17]. A recent consensus guideline on EoE recognized a lower cutoff of 15 or greater eosinophils per HPF for the diagnosis but included the need for compatible esophageal symptoms and, importantly, the exclusion of GERD in establishing a diagnosis of EoE [18].

There is a paucity of data regarding patients with eosinophil density of less than 15 eos per HPF on esophageal biopsies. We have termed this “low grade esophageal eosinophilia.” Little is known about the demographics, clinical symptomatology, and natural history of patients with low grade esophageal eosinophilia. Consequently, the clinical significance, appropriate treatment, and long-term outcomes remain unclear. With this in mind, this investigation sought to determine the clinical significance of low grade esophageal eosinophilia by retrospectively reviewing the clinical experience at Mayo Clinic Rochester with adult patients over a 5-year period.

Methods

The study was approved by the Mayo Foundation Institutional Review Board. A database of 635 patients with eosinophil, eosinophils, or eosinophilia, in the final pathology report from EGD with esophageal biopsy between January 1, 2002 and January 1, 2007 was reviewed. After excluding patients younger than 18 years old, those with greater than 14 eos per HPF on biopsy, and patients with a prior diagnosis of EoE, 59 patients were identified. These patients were compared to a group of 418 patients with greater than or equal to 15 eos per HPF identified during the same time period. Of note, all these reports were completed prior to the consensus definition of EoE. Therefore, these patients met historic criteria for EoE. Specifically, the diagnosis was based on a maximal esophageal eosinophilic density greater than or equal to 15 eos in any HPF.

As per protocol at our institution prior to 2005, all patients had a minimum of four esophageal biopsies obtained from 10 cm proximal to the LES. Further, 31% (18/59) had at least two biopsies obtained from the distal esophagus as well. Biopsy specimens were stained with hematoxylin and eosin and then read by a single experienced GI pathologist (TCS) using Nikon E600 microscopes with 10 × 25 ultra wide eyepieces. The area of greatest eosinophil density was first located by low powered review. Eosinophils were then counted using a 40× objective, a field diameter of 0.625 mm and a field area of 0.307 mm [2]. The peak eosinophil count per HPF was reported.

Pertinent medical history was reviewed. The presence of gastroesophageal reflux was assessed by careful review of

clinician note, endoscopic presence of esophagitis, and patient response to questions regarding the presence of “heartburn” and “regurgitation” on the Mayo Clinic standardized patient questionnaire. If any discrepancy was noted between the physicians note and the questionnaire the physicians’ note was used. Food impaction at our institution is defined as food stuck in the esophagus for greater than 5 minutes [19]. Atopy was defined as a history of allergic rhinitis or asthma. Patients were divided into three groups: those with 1–9 eos per HPF (group A), those with 10–14 eos per HPF (group B), and those with greater than or equal to 15 eos per HPF (group C). Clinical, endoscopic, and histologic findings were compared using the student *t* test and ANOVA for continuous variables and Fisher’s exact test (two-tailed) and chi-square test for categorical variables.

Results

Demographics and Atopy

Fifty-nine adult patients with low grade esophageal eosinophilia, defined as 1–14 eos per HPF, and 418 adult patients with greater than or equal to 15 eos per HPF were identified. All three groups showed a male predominance. The mean age of patients in all three groups was similar and in the fourth decade of life. However, patients with low grade eosinophilia (groups A and B) were older (48 ± 2.1 vs. 43 ± 0.7 years, $P = 0.04$) and less likely to be Caucasian (94.9 vs. 99.5%, $P = 0.02$) than those with classic EoE (group C). Moreover, patients in groups A and B were less likely to have asthma or allergic rhinitis than those in group C (15.3 vs. 34.0%, $P = 0.004$) (Table 1).

Clinical Presentation

Not surprisingly, in this retrospective study, the majority of patients complained of solid food dysphagia at the time of presentation. While patients meeting historical criteria for EoE (group C) were more likely to have dysphagia ($P = 0.02$), there was no difference in the frequency of food impaction between those with low grade esophageal eosinophilia (groups A and B) and those with ≥ 15 eos per HPF (group C). In addition, heartburn was seen at an equal frequency in all three patient groups (Table 2). Twenty-one of 59 patients included in the study were on proton pump inhibitors (PPI) at the time of the index endoscopy.

Endoscopic Findings

Esophagogastroduodenoscopy (EGD) was performed for dysphagia in most patients, with a small subset of patients presenting for other indications. In those patients with low

Table 1 Demographics and atopy

Characteristic	1–9 eos per HPF	10–14 eos per HPF	≥15 eos per HPF	<i>P</i> value ^a [A + B vs. C]	<i>P</i> value ^b [A vs. B vs. C]
Number	23	36	418	–	–
Eos/HPF [mean (range)]	7 (1–8)	10 (10–14)	40 (15–300)	–	–
% male	78% (18/23)	67% (24/36)	73% (307/418)	0.6	0.8
Mean age	47 ± 4	48 ± 3	43 ± 0.7	0.08	0.04
% Caucasian	91% (21/23)	97% (35/36)	99.5% (416/418)	1.0	0.02
Allergic rhinitis	17% (4/23)	14% (5/36)	69% (142/207)	<0.01	<0.01
Asthma	13% (3/23)	14% (5/36)	48% (62/130)	<0.01	<0.01
PPI	26% (6/23)	42% (15/36)	27% (110/407)	0.2	0.2

eos eosinophils, *HPF* high-powered field, *PPI* proton pump inhibitor

^a *P* value for comparison between all three groups (group A vs. group B vs. group C)

^b *P* value for comparison between low level esophageal eosinophilia (groups A and B) versus ≥15 eos per HPF (group C)

Table 2 Symptoms at presentation

Symptoms	1–9 eos per HPF	10–14 eos per HPF	≥15 eos per HPF	<i>P</i> value ^a [A + B vs. C]	<i>P</i> value ^b [A vs. B vs. C]
Dysphagia	91% (21/23)	78% (28/36)	93% (338/363)	0.01	0.02
Solid food dysphagia	70% (16/23)	56% (20/36)	78% (282/363)	0.01	0.01
Food impaction	26% (6/23)	28% (10/36)	33% (121/363)	0.6	0.4
Heartburn	74% (17/23)	64% (23/36)	61% (158/260)	0.4	0.4

eos eosinophils, *HPF* high-powered field

^a *P* value for comparison between all 3 groups (group A vs. group B vs. group C)

^b *P* value for comparison between low level esophageal eosinophilia (groups A and B) versus ≥15 eos per HPF (group C)

grade esophageal eosinophilia (groups A and B), EGD was performed for dysphagia in 81% (48/59) and for emergent food impaction in 5% (3/59). In the remaining cases, EGD was done in 12% (7/59) for gastroesophageal reflux and 2% (1/59) for anemia. In these cases, biopsies were obtained due to an endoscopic appearance consistent with EoE.

Endoscopic findings are summarized in Table 3. The ringed esophagus was the most common endoscopic finding, seen in 32% of patients (155/477) overall. Of note, the ringed esophagus ($P = 0.5$) and any endoscopic features of EoE ($P = 0.7$) were seen in a similar proportion of patients with low grade esophageal eosinophilia (groups A and B) and those with ≥15 eos per HPF (group C) (Table 3).

Follow-Up

Follow-up endoscopy with esophageal biopsies were obtained in 14 patients (23%): ten of whom had continued dysphagia, three with refractory GERD symptoms, and one for follow-up of previous food bolus impaction. Six of the 14 patients were treated with PPI therapy in the interval between the initial and repeat EGD. Overall, mean time to follow-up EGD was 42 weeks (range 8–118 weeks). A total of 36% (5/14) of low grade eosinophilia patients

undergoing repeat endoscopy had 15 eos per HPF or greater on repeat endoscopy.

Topical swallowed aerosolized fluticasone was prescribed to three of the five patients who met criteria for EoE on the subsequent endoscopy. All three of these patients followed-up with a Mayo Clinic provider, with all reporting symptomatic improvement at 8, 10, and 12 weeks, respectively. An additional nine patients with only low level esophageal eosinophilia who did not have a second endoscopy received swallowed topical corticosteroids after initial endoscopy. Seven of the nine patients had follow-up with a Mayo Clinic provider, with six of seven patients reporting improved symptoms at mean follow-up of 8 weeks (range 4–12 weeks). Of the 12 patients treated with topical corticosteroids, four presented with persistent dysphagia on once daily PPI therapy and one on twice daily PPIs.

Follow-up with a Mayo Clinic provider was available in 18 patients not treated with swallowed aerosolized corticosteroids. Thirteen patients were treated with once daily PPI therapy, three with twice daily PPI therapy, and two with dilation and once daily PPI. Symptoms were improved in ten of 13 patients treated with once daily PPI, zero of three patients receiving twice daily PPI, and one of two

Table 3 Endoscopic findings

Findings	1–9 eos per HPF	10–14 eos per HPF	≥15 eos per HPF	<i>P</i> value ^b [A + B vs. C]	<i>P</i> value ^c [A vs. B vs. C]
Ringed esophagus	39% (9/23)	36% (13/36)	32% (133/418)	0.7	0.5
Furrows	13% (3/23)	0% (0/36)	12% (49/418)	0.09	0.2
Non-distal stricture	13% (3/23)	0% (0/36)	5% (21/418)	0.08	1.0
Whitish exudates	0% (0/23)	2% (1/36)	2% (8/418)	0.7	1.0
Findings of EoE ^a	48% (11/23)	39% (14/36)	39% (162/418)	0.8	0.7
≥15 eos per HPF on <i>f/u</i> endoscopy	50% (3/6)	25% (2/8)	N/A	0.3	N/A

eos eosinophils, *HPF* high-powered field, *EoE* eosinophilic esophagitis, *f/u* follow-up

^a Ringed esophagus, furrows, non distal stricture, or whitish exudates on endoscopy

^b *P* value for comparison between all 3 groups (group A vs. group B vs. group C)

^c *P* value for comparison between low level esophageal eosinophilia (groups A and B) versus ≥15 eos per HPF (group C)

patients who underwent balloon dilation and once daily PPI therapy at a mean follow-up of 21 weeks (range 4–60 weeks).

Discussion

Eosinophilic esophagitis is a diagnosis based on clinical and pathological factors. The number of eosinophils on esophageal biopsy required for the diagnosis varies in the literature, with a recent consensus recommending lowering the normal threshold to more than or equal to 15 eos/HPF. The clinical significance of low grade esophageal eosinophilia has not been clearly defined. We retrospectively identified 59 patients with low grade esophageal eosinophilia (1–14 eos per HPF) as well as 418 patients with prominent esophageal eosinophilia (≥15 eos per HPF) to address this question.

Of note, most of the literature on EoE predates the consensus definition. EoE in the literature often was based on higher eosinophil counts, usually with symptoms that started the evaluation. The diagnosis was made using various biopsy protocols, and very often without the exclusion of GERD. This leads to confusion when using the term EoE and referring to literature regarding EoE based on a different definition of the term. We will use the term “historic EoE” when we refer to studies performed prior to the consensus definition. Moreover, this study was completed before the establishment of the current consensus definition of EoE requiring the exclusion of GERD, and before our current knowledge of biopsy protocols. With these reservations, we consider the conclusions from the data here valid and useful.

Patients with low grade esophageal eosinophilia (groups A and B) were similar to those with ≥15 eos per HPF (group C) and those with historic EoE as described in the literature, presenting in the fourth decade of life with a

roughly 3:1 male predominance [2, 8, 9, 17]. The rate of atopy in our cohort of EoE patients was similar to the estimate of 52% in EoE patients described by Sgourous et al. [8] and greater than that seen in patients with low grade esophageal eosinophilia. However, while asthma and allergic rhinitis were strongly associated with an increased esophageal eosinophilic density, it should be acknowledged that the rate of these findings in our cohort of patients with low grade esophageal eosinophilia is greater than that of the general population, with only a 9% baseline prevalence of asthma reported in Olmstead county [20].

While dysphagia was more common in those patients with ≥15 eos per HPF (group C) than those with low grade esophageal eosinophilia (groups A and B), heartburn and food bolus impaction was present in the same proportion of patients regardless of the degree of esophageal eosinophilia and were similar to descriptions of historic EoE in the literature [8, 18]. Dysphagia was present in 83% of patients with low grade esophageal eosinophilia (groups A and B). This by no means implies that dysphagia is present in the majority of patients with low level esophageal eosinophilia. There was selection bias in which patients underwent esophageal biopsy, with the vast majority done for the symptom of dysphagia or for endoscopic findings suggestive of EoE. However, our data does suggest that some patients with dysphagia do have low grade esophageal eosinophilia.

Food impaction is the symptom of most interest with respect to EoE. Food impaction has not been well defined in the literature but is the hallmark symptom of adult EoE. At our institution, food impaction is defined as food stuck for greater than 5 min [19]. Interestingly, in this study food impaction was present in 27% of patients with low level eosinophilia (groups A and B), with 5% of all patients with low grade esophageal eosinophilia requiring endoscopic removal of solid food bolus impaction. Strikingly, these numbers are similar to patients with more pronounced

esophageal eosinophilia (group C). Food impaction has been described in a similar proportion of patients with historic EoE [18]. Further, we have previously shown that food impaction, as defined above, was the only symptom predictive of historic EoE [19].

Characteristic endoscopic findings of EoE, comprising the ringed esophagus, furrows, non distal strictures, or whitish pinpoint exudates were similar among all three groups. Ringed esophagus was the most common finding, seen in 32% of cases overall, and 37% of patients with low grade esophageal eosinophilia. These findings, though not pathognomonic for EoE, are strongly suggestive of historic EoE. In a previous study where we biopsied all patients with dysphagia, the prevalence of any endoscopic finding of EoE (non-distal stricture, white spots, fragility, rings, or furrows) was 33% (11/33) of historic EoE patients using a cut-off of 20 eosinophils/hpf [19]. This frequency is similar to that reported in this patient population

On follow-up, a minority of patients with low grade esophageal eosinophilia had persistent symptoms leading to a repeat upper endoscopy at Mayo Clinic Rochester. More than one-third of these patients were found to have 15 eos per HPF or greater on repeat endoscopy. Further, their dysphagia responded to topical corticosteroid therapy. Moreover, several other low grade eosinophilia patients without repeat endoscopy had resolution of their dysphagia with topical steroid therapy. This suggests some patients with low level eosinophilia may have a similar clinical syndrome to those we classify as historic EoE.

GERD was not excluded in these patients. While heartburn was seen in a similar proportion of patients with low grade esophageal eosinophilia (groups A and B) and those with ≥ 15 eos per HPF, heartburn may not be a highly specific symptom for GERD in patients with EoE. However, our data does support the view that the interrelationship between GERD and EoE needs further exploration [21]. It is very possible that GERD may increase antigen exposure through the acid damaged intramucosal spaces and potentiate esophageal eosinophilia [22]. Although the current EoE definition excludes any overlap between GERD and a syndrome of steroid responsive dysphagia with esophageal eosinophilia, we and others feel this overlap is a real entity [22]. A recent study found not only a similar prevalence of heartburn amongst patients with EoE and those with GERD, but also a large range in eosinophil count with significant overlap amongst patients with EoE and GERD [23]. Thirty percent of our patients with historic EoE had classic erosive esophagitis consistent with GERD, many of which had their dysphagia respond to topical steroids after failing PPI treatment [19]. Over one-half of patients with dysphagia and esophageal eosinophilia in a recent study had abnormal esophageal acid exposure [24]. Six of the 14 patients were on PPI therapy at the time of

repeat EGD; three of these six patients had ≥ 15 eos per HPF on follow-up endoscopy.

The role of PPI therapy in EoE is another confounding factor in this study. Peterson et al. [24] have demonstrated equivalent improvement of dysphagia and esophageal eosinophilic infiltration between PPI therapy and topical corticosteroids in a cohort of EoE patients with a high incidence of pathologic acid reflux. Further recent data from Molina-Infante demonstrated histologic and symptomatic response to PPI therapy in 75% of patients with ≥ 15 eos per HPF [25]. Together, these studies suggest that esophageal eosinophilic infiltration may be PPI responsive and may reflect a subset of either GERD alone or coexistence of GERD and EoE. However, in this study PPI therapy did not affect the likelihood of esophageal infiltration on repeat EGD. Of the six patients on PPI therapy at the time of repeat EGD, three met historical criteria for EoE. Consequently, it is unlikely that those patients who subsequently met historical criteria for EoE represented a subset of patients with GERD.

This study has several limitations. No differences were seen between Groups A and B, suggesting that the density of esophageal eosinophilic infiltration did not affect clinical or endoscopic findings. However, a trend towards a greater frequency of dysphagia, endoscopic furrows, and non distal strictures were seen in Group A compared to Group B (*P* values of 0.3, 0.06, and 0.06, respectively). The clinical significance of this trend is unclear. As mentioned above, this is a highly selected group of patients with low grade eosinophilia; specifically, those that underwent biopsy. This represents significant selection bias and therefore the clinical characteristics of this group may not be representative of all patients with low grade eosinophilia. The incomplete follow-up of patients represents a potential source of error in this study. It is unclear if any specific symptoms affected the choice of therapy given. Histology was not re-reviewed by a single pathologist, and therefore inter-observer variability in this patchy disorder was not assessed.

It is possible these findings are related to sampling error, and more biopsies at the index endoscopy potentially would identify more patients with greater than or equal to 15 eos per HPF. Our technique has changed over time, but for the time period encompassing the study our practice was to obtain at least four esophageal biopsies from at least 10 cm proximal to the squamocolumnar junction. Gonsalves et al. [26] have shown that obtaining five esophageal biopsies provides 100% sensitivity for the diagnosis. However, there was no statistically significant increase in diagnostic yield from biopsy specimen four to five. In addition, distal esophageal biopsies, which were inconsistently obtained in our patients, have consistently shown higher eosinophil counts in historic EoE, with potentially up to 20% of diagnosis being missed by non distal biopsies

alone [26–28]. However, Liacouras et al. [29] diagnosed EoE in 307 of 312 cases by the mid esophageal biopsies. Therefore, while it is possible that some of our patients with low level eosinophilia may have met the eosinophil cut-off of 15 currently used to define EoE, if more biopsies and routine distal esophageal biopsies were obtained, inadequate sampling at most only slightly influence our results and was unlikely to have had any significant effect on our overall conclusions.

In conclusion, some patients with less than 15 eos per HPF may have a similar clinical presentation to patients with historic EoE. Moreover, dysphagia in some patients with low grade esophageal eosinophilia responds to topical steroid therapy and a proportion of these patients are found to have 15 eosinophils/HPF or greater on repeat endoscopy and respond to topical steroid therapy with resolution of dysphagia. Further studies are needed to evaluate patients with low level eosinophilia, but treatment of EoE may be worth considering in selected cases of low grade eosinophilia.

Conflicts of interest None of the authors have conflicts of interests to disclose.

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