Increased Incidence of Eosinophilic Esophagitis in Children and Adults With Celiac Disease

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Goals and Background: Case series have suggested an association between eosinophilic esophagitis (EoE) and celiac disease (CD) in children. We analyzed a cohort of patients with CD to confirm this association in children, and determine whether it extends into adulthood.

Methods: A database of patients with CD was reviewed to determine the number of patients with comorbid diagnoses of EoE. Histopathology reports of esophageal biopsies were reviewed to identify all cases of increased esophageal eosinophilia. Cases of EoE were diagnosed if biopsies revealed ≥ 15 eosinophils per high power field and associated symptoms were present. Age-adjusted and sex-adjusted standardized incidence ratios (SIR) with corresponding 95% confidence intervals (CI) were calculated in comparison to published US population-derived incidence data.

Results: EoE was diagnosed in 4 children and 10 adults. EoE is more common compared with the general population; SIR for children was 35.6 (95% CI, 9.3-79.0) and for adults 13.1 (95% CI, 6.2-22.5). Overall, the age-adjusted and sex-adjusted SIR was 16.0 (95% CI, 8.7-25.5).

Conclusions: The incidence of EoE in our cohort of patients with CD was increased compared with the general population. Coexistent EoE should be considered in patients with CD who have persistent esophageal symptoms.

Key Words: celiac disease, eosinophilic esophagitis, gastrointestinal eosinophilia

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Eosinophilic esophagitis (EoE) and celiac disease (CD) are considered distinct immunologic diseases of the gastrointestinal tract. EoE typically presents with symptoms ranging from failure to thrive and vomiting in children to chest and epigastric pain, dysphagia, and food impaction in older patients.[1] Diagnosis of EoE is based on the presence of symptoms in conjunction with finding ≥ 15 eosinophils per high power field (HPF) in esophageal mucosal biopsy specimens, and the exclusion of other diseases that cause esophageal eosinophilia.[2] A recent study in the US population estimates the prevalence of EoE to stand at 55.0 cases per 100,000 people.[3] In addition, the incidence seems to be increasing in both adults and children, though it is as yet unclear whether this is solely attributable to increasing awareness and detection of the disease or whether it represents a genuine phenomenon.[3–6] Most recently, DeBrosse et al[7] report on their reexamination of esophageal biopsy specimens from a cohort of patients who underwent esophagogastroduodenoscopy (EGD) from 1971 to 1999, found that the incidence of EoE increased over the study period in parallel with rising rates of endoscopy; however, there was a stable proportion of esophageal eosinophilia per EGD when corrected for the large concomitant increase in endoscopy volume. They identified histologic features of EoE in almost 30% of patients who were previously given diagnoses of gastroesophageal reflux disease (GERD), and suggest that the rise in incidence of EoE is largely due to growing recognition of it. From an immunologic perspective, the pathogenesis of EoE is thought to be linked to atopy.[8]

On the other hand, CD is a T-helper (Th) 1-mediated autoimmune disease of the small intestine induced by the ingestion of gluten.[9] CD has classically been diagnosed when duodenal biopsies show typical histologic alterations and a favorable response occurs to a gluten-free diet.[10] Serologic testing using antitissue transglutaminase and antiendomysial antibodies has become a useful adjunct for diagnosis of CD by allowing for noninvasive screening of at-risk populations.[11] Several serologic screening studies have demonstrated that the worldwide prevalence of CD is approximately 1%, though many of those affected remain undiagnosed.[12–14] Patients with CD are known to be at higher risk for coexisting autoimmune diseases, such as type 1 diabetes mellitus and autoimmune thyroiditis,[15] but their risk of developing atopic diseases remains unclear.[16,17]

Recent case reports and cohort studies have suggested an association between CD and EoE in pediatric populations.[18–21] Both diseases are caused by aberrant, but distinct, immune responses to ingested antigens and can be responsive to food elimination diets. In this study, we analyzed a large database of patients with CD to confirm the association between CD and EoE in children, and to determine whether it extends to the adult population.

MATERIALS AND METHODS

This study was conducted at the Celiac Disease Center at Columbia University Medical Center, a referral center in New York City that specializes in the diagnosis and management of CD. The Celiac Disease Center prospectively maintains 2 anonymized databases of patients with

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CD. The database for adults includes patients seen and treated from 1981 to the present time. Similarly, data regarding pediatric patients from 2000 to the present have been entered into a separate database. The diagnosis of CD was confirmed in all patients in these databases based on a combination of serologic data, clinical symptoms, and histopathologic findings on small bowel biopsy (n = 1439). The institutional review board at Columbia University approved the study protocol (7/21/2009). Retrospective analysis of clinical data and all endoscopy reports with associated histopathology reports of biopsies performed at Columbia University Medical Center on these patients with CD for a variety of indications since January 1, 2000 was performed. In pediatric cases, biopsies of the esophagus were usually taken routinely during EGD. Esophageal biopsies of adult patients were taken during EGD at the discretion of the clinician, and were typically done if there were abnormal findings at endoscopy or patients had esophageal symptoms. After the review of all esophageal biopsy histopathology reports, all esophageal biopsies reported to have any degree of increased eosinophils were examined again by the study pathologist (GB). EoE was diagnosed if biopsy specimens from either the lower or middle-third of the esophagus demonstrated ≥ 15 eosinophils per HPF—averaged over 3 representative fields—with evidence of eosinophil clustering and/or microabscess formation and eosinophil degranulation,[2,22] and patients had clinical symptoms of esophageal disease. Symptoms of esophageal disease were defined as a history of food impaction, dysphagia, or symptoms of gastroesophageal reflux or abdominal pain.[2] Our EoE case definition did not require exclusion of GERD by pH monitoring or trial of proton pump inhibitor (PPI) because it was based on the definition used by Prasad et al,[3] whose population served as our comparison group. For patients diagnosed with EoE, the mean numbers of eosinophils averaged over 3 representative fields were also measured in samples of stomach and proximal small intestinal mucosa, where available.

The expected incidence of EoE was calculated for each sex and 10-year age-specific bracket by specific incidence rates from 2001 to 2005 from unpublished raw data collected by Prasad et al[3] in an Olmsted County population-based study of EoE. Patient years at risk were calculated from the date of CD diagnosis to the date of diagnosis of EoE or from the date of EoE diagnosis to the date of CD diagnosis, depending on which diagnosis was made initially. Expected values for the number of patients with EoE were weighted by the age-adjusted person years contributed by the individuals in the data set.[23] Standardized incidence ratios (SIR) (ratio of observed to expected) and the matching 95% confidence intervals (CI) were calculated using the assumption that the observed incidence of EoE had a Poisson distribution. Patients with comorbid diagnoses of EoE and CD were compared with those having CD alone with regards to age, sex, and timing of diagnosis using the unpaired t test and Fisher exact test. Univariate analysis of duodenal eosinophilia in relation to dyspeptic symptoms in patients with both EoE and CD was performed using the Mann-Whitney U test.

RESULTS

Of the 1439 patients with CD in the combined databases, 962 were female and 477 were male. There were 1142 adults and 297 children. The total number of EGDs available for review was 1044, and the number of individual patients with esophageal biopsies performed on at least 1 endoscopy was 518. In total, 666 esophageal biopsies were reviewed. Four children (2 male, 2 female) and 10 adults (6 male, 4 female) were found to have EoE based on the criteria described in the Materials and Methods section (Table 1). The age-adjusted and sex-adjusted SIR of EoE in patients with CD was 16.0 (95% CI, 8.7-25.5). In female patients, the SIR was 11.8 (95% CI, 4.3-23.2); in male patients, the SIR was 21.8 (95% CI, 9.3-39.5). For the pediatric population with CD, the overall SIR of EoE was 35.6 (95% CI, 9.3-79.0). In adults with CD, the SIR of EoE was 13.1 (95% CI, 6.2-22.5).

Two additional cases of probable EoE were identified (1 male child and 1 female adult) based on the presence of significant esophageal eosinophilia (average 90/HPF and 40/HPF, respectively, with clusters of eosinophils and/or microabscesses and eosinophilic degranulation); however, they were not included in the group of "definite" cases, as clinical documentation did not record significant esophageal symptoms. On addition of these 2 cases of EoE in the calculations, the SIR of EoE in patients with CD rose to 44.5 (95% CI, 14.0-92.0) and 14.4 (95% CI, 7.2-24.2) in pediatric and adult populations, respectively.

Despite the known predisposition of the female sex to develop CD and male sex to develop EoE, the sex proportions of patients with comorbid diagnoses did not differ significantly from the gender proportions of the patients with CD alone in children or adults. The group of children with both EoE and CD comprised of 50% female population in comparison to the 59% female population with CD ($P = 1.00$). The adult cohort with EoE and CD was 60% male, compared with 44% men in the cohort with CD alone ($P = 0.08$).

TABLE 1. Standardized Incidence Ratios

Cohort	No. Patients With Celiac Disease	No. Patients-years of Observation	Observed No. EoE Cases	Expected No. EoE Cases*	SIR	95% CI
Male	477	4258.2	8	0.36743	21.8	9.3-39.5
Female	962	8991.5	6	0.50721	11.8	4.3-23.2
Children (age 0-19 y)	297	2439.5	4	0.11244	35.6	9.3-79.0
Adults (age ≥ 20 y)	1142	10810.4	10	0.76219	13.1	6.2-22.5
Total	1439	13249.8	14	0.87464	16.0	8.7-25.5

*Calculated based on incidence rates from data collected by Prasad et al[3] in a population-based study from Rochester, MN.

CI indicates confidence interval; EoE, eosinophilic esophagitis; SIR, standardized incidence ratio (observed/expected number of cases of EoE based on population data).

The average age of the pediatric patients with CD when diagnosed with EoE tended to be younger than the average age of the overall pediatric CD cohort: 8 ± 3.3 versus 12 ± 4.0 years ($P = 0.07$). In the adult cohort of patients with CD, those with both diseases were younger at the age of diagnosis of EoE (41 ± 14.9 y) than the average age of individuals only with CD (53 ± 18.0 y, $P = 0.04$).

There was a trend toward pediatric patients being more likely to have been diagnosed simultaneously with EoE and CD ($3/4 = 75\%$) compared with the adult patients ($2/10 = 20\%$), though this did not reach statistical significance ($P = 0.09$). The majority of the adult patients were diagnosed with EoE after their diagnosis of CD, with a mean duration of 7.2 ± 6.0 years of CD before diagnosis of EoE. The lone pediatric patient who was not diagnosed simultaneously with EoE and CD actually had pathologic findings diagnostic of EoE 4 years before his diagnosis of CD (identified retrospectively on review of pathology slides). In our cohort, pediatric patients more commonly complained of abdominal pain (3 of 4), whereas persistent heartburn and dysphagia were noted more often in the adult population (9 of 10) (Table 2).

Our patients had eosinophilia in biopsies from other parts of their upper gastrointestinal tract. Eosinophilia was noted in both the stomach and duodenal biopsies of many of our patients, however, it was more prominent in the duodenum (Table 2). In light of reports that duodenal eosinophilia has been associated with dyspepsia,[24] we analyzed whether this symptom was associated with the degree of duodenal eosinophilia in our patients. The mean number of duodenal eosinophils per HPF among patients with dyspepsia was 35.6, which was not significantly different from the number among those without dyspepsia (33.1, $P = 0.91$ by Mann-Whitney U Test). Gastric eosinophilia was much more variable with a mean of 16.2 eosinophils per HPF with a standard deviation of 26.8 eosinophils per HPF (median 3 eosinophils/HPF). Only 2 of the 12 samples available for review reached a threshold value of ≥ 30 eosinophils/HPF, beyond which a diagnosis of "histologic eosinophilic gastritis" might be considered.[25]

Six of our patients had earlier biopsies with pathologic features meeting our diagnostic criteria of EoE, preceding the biopsies that were reported as diagnostic of EoE. This led us to revise our dates of diagnosis (average time between initial biopsy and subsequent diagnosis was 3.9 ± 2.2 y).

Degree of compliance with a gluten-free diet was not documented in a standardized manner in the clinical records, therefore, we are limited in our ability to make statements about the effects of gluten exposure on the course of EoE. However, patients 8, 9, and 11 all had follow-up endoscopies while they were on a gluten-free diet for previously diagnosed CD. In these patients, duodenal pathology had normalized (Marsh 0 in all patients), but esophageal eosinophilia was persistent (esophageal biopsies with >100 eosinophils/HPF averaged over 3 fields in at least 1 sample). In this small series, a gluten-free diet did not seem to have any effect on the histologic features of EoE.

Of the 8 patients with follow-up histologic data, there was a mean follow-up time of 3.32 ± 1.87 years. Five of the patients were not on specific therapy for EoE at the time of their later endoscopies because their eosinophilia was initially reported as consistent with reflux esophagitis. The majority of these patients were treated with PPI (4 of 5) until their later endoscopies revealed even greater degrees of esophageal eosinophilia and a formal diagnosis of EoE was made. The pediatric patient among these 5 had duodenal crypt hyperplasia at his initial endoscopy, and was only diagnosed with CD at his second endoscopy where he had Marsh 3c lesions in the duodenum. He was the sole patient in our cohort to have features of EoE predate his diagnosis of CD. Table 3 shows the clinical course of EoE in those 3 patients with available data, who were recognized to have EoE and treated specifically for it during the time frame of this study. In these few patients, the clinical course of EoE seemed to be independent of the clinical course of CD as defined by symptoms and histology.

DISCUSSION

Previous case reports and cohort studies have suggested a relationship between CD and EoE in pediatric

TABLE 2. Clinical and Histopathologic Characteristics of Patients With Celiac Disease With Eosinophilic Esophagitis

Patient	Sex	Age at Diagnosis (y)	Presenting Symptoms	Eos/HPF* Proximal/Mid or Distal Esophagus	Eos/HPF* Duodenum	Duodenal Pathology at Time of Esophageal Biopsy (MARSH Score)†
1	M	6	Abdominal pain	—/16	28	Crypt hyperplasia (Marsh N/A)
2	M	6	Abdominal pain	—/56 clusters	20	Marsh 3a
3	F	7	Abdominal pain	—/65	54	Marsh 3b
4	F	13	Dysphagia, abdominal pain	—/120 clusters	57	Marsh 3a
5	F	22	Dyspepsia	—/24	19	Marsh 3b
6	F	23	Reflux	—/17	42	Marsh 1
7	M	28	Reflux	—/27	58	Marsh 3c
8	M	32	Dysphagia	3/22	13	Marsh 0
9	M	35	Dysphagia	2/106 clusters	25	Crypt hyperplasia (Marsh N/A)
10	F	44	Dysphagia	122 clusters/67 clusters	42	Marsh 3a
11	M	50	Reflux, dysphagia	—/107 clusters	32	Marsh 3a
12	M	53	Dysphagia	36/51 clusters	2	Marsh 2
13	F	57	Reflux	128/110 clusters	68	Marsh 3a
14	M	64	Reflux, dysphagia	80/66	21	Marsh 0

*Note that the numbers represent means of counts over 3 representative HPF examined.
†Marsh score requires intraepithelial lymphocytosis.
Eos indicates eosinophils; F, female; HPF, high power field; M, male; N/A, not applicable.

TABLE 3. Clinical Course of Patients With Celiac Disease With Eosinophilic Esophagitis

Patient	Treatment	Time After Initial Diagnosis of EoE (y)	Symptoms	Eos/ HPF*Proximal Esophagus	Eos/HPF*Mid or Distal Esophagus	Duodenal Pathology at Time of Esophageal Biopsy (Marsh Score)
4	PPI†	0.8	Dysphagia	161 with clusters	113	Marsh 3a
	On swallowed fluticasone	1.7	Minimal symptoms	0	0	Marsh 0
	PPI, weaned off of fluticasone	4.2	Abdominal pain and dysphagia	70	70	Marsh 3a
8	PPI†	3.4	Dysphagia	142	106	Marsh 0
	PPI, food elimination (gluten/fish)	5.6	Dysphagia improved	1	36	Marsh 3a
10	PPI, swallowed fluticasone, Cromolyn	0.3	Abdominal pain	—	0	Marsh 3a

*Note that the numbers represent means of counts over 3 representative HPF examined.
†Not on therapy directly targeted against EoE as previous biopsies not reported as EoE.
EoE indicates eosinophilic esophagitis; Eos, eosinophils; HPF, high power field; PPI, proton pump inhibitor.

patients in Italy and Australia. However, these studies have been limited by small sample sizes and none of them have addressed whether this association continues into adulthood.[18–21] The results of our study demonstrate a clear association between CD and EoE in both pediatric and adult populations, and is the first to quantify this association in direct comparison to population-based incidence rates.

We acknowledge that there are several limitations to our approach. First, we have compared the attendees of a specialized clinic at a tertiary care referral institution to the general population. However, given the dearth of population-based data on EoE, this comparison represents the best approximation available, and even if such an approximation is an overestimation, the magnitude of the increase in incidence rate [SIR 16.0 (95% CI, 8.7-25.5)] argues that this is a true association. Second, EoE by definition requires endoscopic evaluation and biopsy to establish the diagnosis. Patients with CD, by virtue of their disease and being in the long-term care of a gastroenterologist, are more likely to undergo repeated upper endoscopy with biopsy. Again, although it is possible to attribute some measure of the increased incidence of EoE in this population to detection bias from increased biopsy surveillance and sampling, especially in children as routine esophageal biopsies are often taken, detection bias alone is unlikely to account for the entirety of the degree of increase in incidence of EoE that we observe. Indeed, the degree of association may represent an underestimation, as only a small fraction (518 of 1439, 36%) of our entire cohort underwent esophageal biopsy. Third, comparisons of incidence rates of EoE between the general population and our CD cohort could be confounded by the noted increasing incidence of EoE in the general population over the past 3 decades that parallels the increasing upper endoscopy volume.[3] We attempted to mitigate any bias this might introduce by using incidence rates calculated from 2001 to 2005, the time frame that most closely matched the time frame of the data collected in our study. Fourth, our study is retrospective in nature and is constrained by the data documented in clinical records.

Esophageal eosinophilia can occur in many settings, including GERD.[2] The present guidelines for clinical diagnosis of EoE typically recommend exclusion of GERD through intraesophageal pH monitoring or endoscopy with biopsy after treatment with high-dose PPI.[2] Our case definition of EoE did not require the exclusion of GERD as it was modeled on the case definition of EoE used in our comparison population, and because data on use of PPIs and/or intraesophageal pH monitoring was not systematically included in our database of patients with CD. Moreover, it is becoming clear that the relationship between GERD and EoE is probably more complex than these guidelines suggest, and that the diagnoses may not necessarily be mutually exclusive, nor be easily distinguished using the means described.[26–28] Though it is possible that patients with esophageal eosinophilia solely due to GERD could have been misclassified in our study, at least 8 of our 14 patients with EoE were known to be on a PPI at the time of their initial biopsies, and many of the biopsies were from the proximal esophagus, had more than borderline eosinophilia (often in excess of 24/HPF), and also showed other features, such as eosinophilic microabscesses/clusters, degranulating eosinophils, and cytoplasmic vacuolation, which are more consistent with EoE than GERD.[2,22] Eosinophils are considered a normal resident of every portion of the gastrointestinal tract except for in the esophagus where their presence is always pathologic.[29] Mild expansions of the eosinophil population are well known to occur in the duodenum of patients with CD,[30] and this finding was confirmed in our study. On the other hand, we found gastric eosinophilia exceeding the threshold of ≥ 30 eosinophils/HPF, which might indicate "histologic" eosinophilic gastritis[25] in only 2 of our patients, which argues that our observations are not likely to be solely a reflection of increased overall gastrointestinal eosinophilia in the setting of CD.

Despite these limitations, it seems clear from our data that there is an association between EoE and CD that goes beyond simply increased detection, and previous researchers have suggested that this could be due to more general effects of disordered immune regulation.[8,21] EoE is

considered to be caused by an allergic response to ingested antigens. It is known in children to improve with elemental and food elimination diets,[31,32] though it can be difficult to determine the exact food allergen responsible despite using a combination of skin-prick and atopy patch testing.[2] In patients with both EoE and CD, initial reports suggested that the food antigen responsible for both diseases might be gluten. Quaglietta et al,[19] described 6 children with concurrent disease who had symptomatic improvement on a gluten-free diet, and the 3 who underwent follow-up endoscopy with esophageal biopsies had histologic remission, with a mean esophageal eosinophil count of ≤ 10/HPF. Other reports have been less consistent, for example, in the study by Verzegnassi et al,[18] the pathologic features of EoE resolved on a gluten-free diet in only 1 of their 3 patients with concomitant EoE and CD. Studies by both Ooi et al[20] and Leslie et al[21] described resolution of the duodenal mucosal changes on a gluten-free diet, but persistence of the esophageal eosinophilia. We have limited follow-up data on the children in our cohort; however, the majority of our adult patients were all diagnosed with EoE well after having received an established diagnosis of CD and developed EoE while already on a gluten-free diet. Several of the endoscopies at which EoE was diagnosed have evidence of concomitant advanced duodenal histology. In some of the patients, particularly the children, this was due to undiagnosed CD; however, in our patients with known CD, these findings may be due to dietary indiscretion or may also reflect that histologic recovery in CD is often slow and may be incomplete.[33] In addition, in the few cases where serial endoscopic and histologic data were available, florid esophageal eosinophilia was present even while the patients with CD had normal duodenal villous histology.

Taken together, the evidence suggests that the esophageal eosinophilia in the setting of concomitant CD is independent of gluten as the inciting antigen. Certain factors including epithelial stress-induced ligands, such as major histocompatibility class I chain-related molecule A and interleukin-15, are known to induce intraepithelial lymphocyte activation in CD[34–37] and have also been shown to be overexpressed in transcriptomic analysis of patients with EoE.[38] CD is considered to be an autoimmune disease with a prototypical Th1-mediated response, whereas EoE as an atopic disease is thought to be Th2-mediated. Traditionally, Th1 and Th2 immune responses have been considered mutually antagonistic; however, recent studies have suggested that Th1 and Th2-mediated diseases may often coexist due to factors that cause generalized immune dysregulation.[39,40] Both Th1 and Th2 responses have been detected in patients with CD[41] and it is conceivable that the immune response in some individuals might trigger eosinophilic allergic reactions to food antigens other than gluten, thereby predisposing patients with CD to EoE. The relationship of CD with other allergic conditions remains uncertain. Zauli et al[17] reported that undiagnosed silent CD was increased in a cohort of atopic individuals; however, there was no increased rate of allergic conditions in an Italian study of adults with CD.[16]

It is notable that 6 of our patients with CD were not clinically diagnosed with EoE for an average of 3.9 years after initial biopsies that showed substantial esophageal eosinophilia. This suggests that EoE could be underdiagnosed in patients with CD. This could be because there is a variable time between appearance of histopathologic findings and onset of symptoms. Alternatively, a lack of routine esophageal biopsies—particularly in adults—or a low index of suspicion, or perhaps even the failure of recognition of EoE by the pathologist when the biopsy specimens only have moderate degrees of esophageal eosinophilia may also contribute. The lag in diagnosis time may also, in part, reflect the recent recognition of EoE as a distinct clinical entity with defined histopathologic features.[7,22]

In summary, our cohort of patients with CD showed a significant increase in the incidence of EoE compared with the general population. This association should prompt clinicians caring for patients with CD to have a heightened suspicion for EoE among those patients with suggestive symptoms such as dysphagia or persistent reflux, and vice versa. The recognition that EoE occurs in patients with CD may lead to greater insights into the complex interplay between environmental factors and host immunity that occurs commonly in many gastrointestinal disorders.

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