ScienceForecast
A digital science library

Research Article
Published: 28 Aug, 2020

SF Hepatology and Gastroenterology

Significance of Esophageal Eosinophilia in Children with Crohn's Disease

Gunasekaran VS[1], Wild Y[2], Schwartz A[3], Heyman MB[2] and Verstraete S[2]*

[1]Medical College of Wisconsin, USA

[2]Department of Pediatric Gastroenterology, University of California San Francisco, USA

[3]Department of Medical Education, University of Illinois at Chicago, USA

Abstract

Background: Studies document an association between Crohn's Disease (CD) and Esophageal Eosinophilia (EE), but its consequences are not yet clear.

Aims: Compare a group of children with CD and EE (EE+) with a control group without EE (EE-).

Methods: We performed a retrospective chart review of 148 pediatric patients with CD seen at the University of California San Francisco Pediatric Inflammatory Bowel Disease Program between February 2003 and May 2016. EE was defined as >15 eosinophils/HPF on at least one esophageal biopsy. Data were collected for gender, race, ethnicity, age, age at CD diagnosis, Physician's Global Assessment (PGA) of CD, Paris Classification for CD location, laboratory values (hematocrit, CRP, ESR, albumin), and medication exposure (immunomodulators, biologics or 5ASA). Patients with esophageal symptoms of EoE were excluded from our study. Characteristics of groups were compared using Fisher's exact tests, $\chi 2$ tests, t-tests, and multivariate logistic regression as appropriate.

Results: CD patients with EE+ had more penetrating and/or stricturing disease (B2, B3, or B2B3) and higher albumin levels compared with EE-. Growth delay was worse in EE+ patients. Both groups had male predominance and similar location of CD.

Conclusion: CD patients with EE+ had more stricturing and penetrating disease, higher albumin levels, and increased likelihood of growth delay compared with EE-. Larger, prospective studies are needed to confirm these observations.

Keywords: IBD; Eosinophilic esophagitis; Esophagus; Inflammatory bowel disease; Eosinophils

Abbreviations

CD: Crohns Disease; EE: Esophageal Eosinophilia; PGA: Physicians Global Assessment; GI: Gastrointestinal; Th2: T Helper Type 2 Cells; IL-5: Interleukin 5; Th1: T Helper Type 1 Cells; Th17: T Helper 17 cells; EGD: Esopha Gogastroduo Denoscopy; ESR: Erythrocyte Sedimentation Rate; IBD; Inflammatory Bowel Disease

Introduction

Eosinophils in the esophagus, or Esophageal Eosinophilia (EE) is associated primarily with esophageal disorders like Eosinophilic Esophagitis (EoE) or gastroesophageal reflux. In addition, EE is also seen in other Gastrointestinal (GI) disorders; Crohn's Disease (CD), celiac disease, achalasia, hyper eosinophilic syndrome, etc [1,2]. The significance of EE in these non-allergic gastrointestinal disorders is not clearly known. Hence it is thought provoking to know the significance of EE in CD. So as a first step, we sought to evaluate the prevalence of EE in pediatric CD. To understand the significance of EE in CD, we need to understand the pathogenesis of EoE and CD. EoE is thought to arise from antigenic, food-derived or environmental proteins that trigger an adaptive immunity, T-helper type 2 (Th2) cell-mediated response, resulting in eosinophilic inflammation. This leads to increased cytokine production, including interleukin-5 (IL-5) and eotaxins [3-5]. EoE remained a rare disease in the past, however its prevalence has increased significantly over the past two decades with pediatric prevalence estimated up to 43/100,000, and is more common in Caucasian males [6]. CD, also an inflammatory disease of the GI tract, has noncaseating granuloma as the pathognomonic finding. The pathogenesis of CD is multifactorial; alterations in the mucosal immune response including T-helper, type 1 (Th1) and type 17 (Th17) cell-mediated responses, genetic predisposition,

OPEN ACCESS

Correspondence:
Vimal Gunasekaran, Medical College of Wisconsin, Wauwatosa, Wisconsin, USA.
Tel: 847-217-1890
E-mail: vgunasekaran@mcw.edu

Received Date: *19 Jul 2020*
Accepted Date: *24 Aug 2020*
Published Date: *28 Aug 2020*

Citation: *Gunasekaran VS, Wild Y, Schwartz A, Heyman MB, Verstraete S. Significance of Esophageal Eosinophilia in Children with Crohn's Disease. SF Hepatol Gastroenterol. 2020; 1(1): 1001.*

and the interaction with the gut microbial flora [7-10]. While EoE is confined to the esophagus, CD affects any part of the digestive tract. In spite of these stark differences in the site(s) of involvement and pathogenesis between CD and EoE, there are similarities and overlap between these two diseases; increasing epidemiologic trends, diagnostic considerations and therapeutic response [9]. A study from South Carolina, USA, demonstrated a high prevalence of CD among pediatric and adolescent patients with EoE. Furthermore, a case series of pediatric patients with inflammatory bowel disease reported the development of EoE, but the study did not elucidate an immunologic or genetic component to explain the overlap of the two diseases [10,11]. These studies showed the co-occurrence of EE or EoE in inflammatory bowel diseases but did not explain the significance of EE in CD patients. Hence, our study aim focuses to explore the occurrence and significance of this unique association, EE in CD.

Methods

Population

Pediatric patients with CD seen at the Pediatric Inflammatory Bowel Disease Program, University of California Benioff Children's Hospital, San Francisco, between February 2003 and May 2016, and ages 1-18 years diagnosed with CD were included in this retrospective study. Patients were divided into two groups, EE+ (CD with esophageal eosinophilia >15/hpf) and EE- (CD without esophageal eosinophilia <15/hpf). To include EE patients and not EoE, we excluded patients with dysphagia or food impaction, as an esophageal dysfunction symptom of EoE.

Study design

All patients had at least one Esopha Gogastro Duodenoscopy (EGD), one colonoscopy and no history of prior intestinal resection. EGD with biopsies is done as a routine in evaluation of inflammatory bowel diseases in pediatric gastroenterology practice, and a minimum of two biopsies were obtained each from the distal and proximal esophagus, stomach and duodenum. From colonoscopy, a minimum of two biopsies was obtained each from the ileum, cecum, ascending, transverse, descending and rectosigmoid colon and assessed separately. Histology reports of these biopsies were reviewed from electronic health records, including esophageal biopsies for presence or absence of eosinophils. Evaluation of eosinophils in the stomach, duodenum and colon was not taken into consideration, as these data were reported inconsistently. Patient data was collected from Improve Care Now. We collected the following data; age, gender, race, and ethnicity. Information regarding assessment and management of CD including Physicians Global Assessment (PGA) (quiescent, mild, moderate or severe activity), age at CD diagnosis, CD location including perianal disease, CD behavior (stricturing, penetrating, or inflammatory), and presence of growth delay were obtained [11,12]. The following laboratory values were collected; hematocrit, C-reactive protein (CRP), Erythrocyte Sedimentation Rate (ESR), and serum albumin level. Use of immunomodulatory medications, biologic agents, and 5-ASA for treatment were a yes or a no response.

Statistical analyses

Categorical variables were compared between groups using Fisher's exact test (for dichotomous variables) or χ^2 (for polychotomous variables); continuous variables were compared between groups using t-tests. Multivariate logistical regression was performed considering clinically significant confounders. Statistical analyses were performed using Stata with p value <0.05 considered significant. Data are shown as mean±SD. Institutional Review Board Approval was granted by the UCSF Human Research Protection Program.

Table 1: Demographics.

	EE+[a] n (%)	EE-[b] n (%)	p	Overall n (%)
N	15	133		148
Male	13 (86.7)	80 (60.2)	0.083	93 (62.8)
Race				
Caucasian	12 (80.0)	79 (59.4)	0.222	91 (61.5)
African American	0 (0.0)	5 (3.8)	-	5 (3.4)
Asian	1 (6.7)	8 (6.0)	-	9 (6.1)
Unknown	0 (0.0)	7 (5.3)	-	7 (4.7)
Other	2 (13.3)	30 (22.6)	-	32 (21.6)
Hispanic Ethnicity	1 (6.7)	20 (15.0)	0.446	21 (14.2)
Age (mean ± SD)	18.98 ±4.16	16.76 ± 4.19	0.054	16.99 ± 4.23
Age at CD Dx (mean ±SD)	10.34 ± 5.09	11.49 ± 3.64	0.269	11.37 ± 3.80

[a]Crohn's Disease patients with Esophageal Eosinophilia; [b]Crohn'sDisease patients without Esophageal Eosinophilia

Results

Demographics

We included 148 patients with CD; age range was 1.3 to 18.6 years (11.37±3.80). Within this cohort 15 (10.1%) patients had eosinophilia (>15/hpf) (EE+); of these, 13 (87.7%) were male. The remainder of our 133 CD patients were considered controls. The age of the patients and age at time of diagnosis of CD were similar in both groups. Complete demographic results are reported in (Table 1). Paris Classification of CD Results (Table 2) [12].

Location

Terminal ileal and colonic locations of disease were more common in EE+, ileocolonic was equally distributed, and upper GI disease was too infrequent to compare. However, none of these

Table 2: Paris classification results.

	EE+[a] n (%)	EE-[b] n (%)	p	Overall n (%)
N	15	133	-	148
Location				
L1[c]	1 (7.1)	5 (4.1)	-	6 (4.4)
L2[d]	4 (28.6)	16 (13.0)	0.245	20 (14.6)
L3[e]	4 (28.6)	38 (30.9)	-	42 (30.7)
L4a[f]	0	2 (1.6)	-	2 (1.5)
L4b[g]	0	1 (0.8)	-	1 (0.7)
Behavior				
B1[h]	12 (80.0)	118 (90.1)	-	130 (89.0)
B2[i]	0	7 (5.3)	-	7 (4.8)
B3[j]	0	2 (1.5)	-	2 (1.4)
B2B3[k]	3 (20.0)	4 (3.1)	0.023	1 (0.7)
Perianal Disease	5 (33.3)	29 (21.8)	0.495	34 (23.0)
Growth Delay	3 (20.0)	7 (5.3)	0.033	10 (6.8)

[a]Crohn's Disease patients with Esophageal Eosinophilia; [b]Crohn'sDisease patients without Esophageal Eosinophilia; [c]Distal 1/3 ileum/limited cecal disease; [d]Colonic; [e]Ileocolonic; [f]Upper disease proximal to ligament of Treitz; [g]Upper disease diastal to ligament of Treitz and proximal to distal 1/3 ileum; [h]Nonstricturing-nonpenetrating; [i]Stricturing; [j]Penetrating; [k]Both Penetrating and stricturing, either at same time or different time.

Table 3: Physician Global Impression of CD.

	EE+[a] n (%)	EE-[b] n (%)	p	Overall n (%)
N	15	133	-	148
Quiescent	9 (60.0)	103 (77.4)	-	112 (75.7)
Mild	6 (40.0)	22 (16.5)	0.064	28 (18.9)
Moderate	0	8	-	8 (5.4)

[a]Crohn's Disease patients with Esophageal Eosinophilia; [b]Crohn'sDisease patients without Esophageal Eosinophilia

Table 4: Laboratory values and treatment response.

	EE+[a] n (%)	EE-[b] n (%)	p
N	15	133	-
Hematocrit (Mean ± SD)	40.15 ± 2.82	38.77 ± 4.34	0.245
CRP (Mean ± SD)	6.95 ± 15.87	6.11 ± 11.39	0.818
ESR (Mean ± SD)	9.99 ± 14.34	15.72 ± 17.53	0.245
Albumin (Mean ± SD)	4.33 ± 0.47	4.06 ± 0.45	0.030
Immunomodulators (%)	7 (46.7)	60 (45.1)	1.0
Biologics (%)	8 (53.3)	75 (56.4)	1.0
5 ASAs (%)	10 (66.7)	51 (38.3)	0.035

[a]Crohn's Disease patients with Esophageal Eosinophilia; [b]Crohn'sDisease patients without Esophageal Eosinophilia

differences reached statistical significance.

Behavior

Stricturing and penetrating diseases were more common and significant in the EE+ group (p=0.023).

Growth

Growth delay was more common in the EE+ group, (p=0.033). This relationship persisted even after adjusting for confounding variables (OR 23.9, CI. 1.54-368.2). Physicians Global Assessment (Table 3): The PGA did not differ between groups, as assessed at their last visit. Laboratory Values (Table 4). The mean of serum albumin was significantly higher in the EE+ group 4.33±0.47 compared to the EE- group 4.06±0.45 (p=0.030). This relationship remained after adjusting for PGA, gender, race and age at Dx (OR 7.9, C.I. 1.43-44.2).

Treatment

Table 4 Patients with EE were more likely to be on a 5-ASA medication (66.7% versus 38.3% in the EE- group [p=0.035]). No differences were documented in immunomodulators or biologic agents between the two groups.

Discussion

Our study shows that 10.1 % of our pediatric patients with CD are EE+. Patients with CD and EE+ are more likely to exhibit growth delay and have a more aggressive phenotype of CD, specifically stricturing and penetrating disease, than CD patients who do not have EE. This association between esophageal eosinophilia and its significance in CD has not been well studied previously, and our data are among the first to suggest this unique association. We also found that our pediatric patients with CD and EE+ have higher albumin levels compared with patients with CD and EE-. While this relationship is statistically significant it does not seem to be clinically significant, since albumin levels in both groups of patients were within normal range (EE+ 4.33±0.47 *versus* EE- 4.06±0.45). Fecal calprotectin has only become a standard test in the last few years, and so data were not available for our retrospective patient groups and so was not part of the analysis. Future studies examining differences in fecal calprotectin might provide further useful information regarding inflammatory markers within the gastrointestinal tract. Other inflammatory markers such as ESR and CRP did not significantly differ between the groups. While the presence of eosinophils in the GI tract in healthy individuals has been established, the specific roles of these cells in gastrointestinal disorders are uncertain. Pensabene et al., reviewed 69 children with colonic eosinophilia and showed that 33% had Irritable Bowel Syndrome (IBS), 32% had Inflammatory Bowel Disease (IBD), of which 54.5% had CD, 10% had food allergies, and 25% had other diagnoses. Within the IBD group, the authors found that the maximum eosinophils per crypt area was significantly higher and also had higher eosinophils in the lamina propria [13]. In addition to the colon, the significance of eosinophils may differ in other parts of the gastrointestinal tract. Talley et al, reported increased eosinophils in the duodenum of non-ulcer dyspepsia patients compared with controls and posited that eosinophils in the duodenum may lead to dysmotility resulting in symptoms of non-ulcer dyspepsia, a functional GI disorder [14]. The EoE consensus guidelines and its recent revision in 2018 supports the observation that EE is a histological finding, while EoE is a specific disease with histological findings of EE and symptoms of esophageal dysfunction. In adults with EoE, dysphagia or food impaction are primary esophageal dysfunction symptoms. Children with EoEcan present with feeding difficulties, gastroesophageal reflux-like symptoms or abdominal pain [1,2]. In our retrospective study, it is difficult to determine if the symptoms of abdominal pain, regurgitation and vomiting in patients with CD are indeed related to CD or related to EoE or simply to EE. Despite the consensus statement including abdominal pain as a symptom of EoE, there is evidence to challenge if abdominal pain is truly a symptom of EoE [15,16]. Hence, we took dysphagia with or without food impaction alone as related to esophageal dysfunction symptom secondary to EoE; thus none of the patients in our study had EoE. Future studies should include all EoE symptoms prospectively, so that CD patients with EE and EoE can all be captured and analyzed. While its curious to know the significance of this association its more so to know the underlying pathophysiology. A study from an internationally recognized EoE center compared 621 EoE patients and [4,8,14] IBD patients to determine if there were any significant relationships between the cohorts. Of these, 35 patients had an ICD code for both diseases and 12 to have overlapping IBD and esophageal eosinophilia. The prevalence of esophageal eosinophilia in IBD was 12/4814 (0.25%), and the prevalence of confirmed EoE in IBD was 5/4,814 (0.10%). There were no substantial clinical, endoscopic, or histologic differences between EoE patients with and without IBD. The authors concluded the prevalence of esophageal eosinophilia in IBD is five times higher than expected in the general population (0.25 *vs.* 0.05%) and EoE in IBD is two times higher than expected (0.10 *vs.* 0.05%).17. Another study on longitudinal analysis of insurance claims data from over 130 million USA patients, found a 3-5 fold increased risk for EoE in patients with IBD compared with individuals without either disease. There was also a 3-6 fold increased risk for IBD in patients with known EoE compared with individuals without EoE. This study showed IBD complications were slightly more common in patients with concurrent EoE, while conversely, patients with EoE were less likely to have complications if they had concurrent IBD [18]. The latter might be explained by the use of immunomodulators (including steroids) in patients with IBD, which would also suppress eosinophils in the esophagus and thus the severity of EoE is lessened. This study adds to the evidence, like ours, that the presence of eosinophils as part of EoE increases the complications

or severity of IBD but the pathophysiology of this "enhancement" is not clear. Our study showed that patients on ASA were EE+ and this was significant. This raises the possibility if mesalamine by its drug sensitivity be a reason for EE positivity [18]. Our study is the first to show the significance of the presence of eosinophils in the esophagus in pediatric patients with CD. Limitations include that this is a retrospective study, has relatively low patient numbers, and the biopsies were not prospectively performed, since a minimum of six biopsies are required to have a diagnosis of EoE and as such should be done for proper EE+ classification. Activity of the CD per Paris Classification was captured at the most recent office visit and not at diagnosis. In addition, it would have been more significant if all patients with any increase in eosinophils in the esophagus i.e., patients who had between 1-14 eosinophils, were captured and categorized. However, it has been the practice of our pathologist to report only if the eosinophils are at or over 15 per high-power field. Future studies should examine any increase in eosinophils in the esophagus, categorize according to eosinophilic density, and correlate with the features of CD. In conclusion, we showed 10.1% of pediatric patients with CD children are EE+. The presence of EE in these patients is associated more with stricturing and penetrating disease and have associated growth delay. It is not clear if EE is a manifestation of EoE, nor if these eosinophils increase the severity of CD. We excluded patients with esophageal symptoms, and so our patients with EE do not meet diagnostic criteria for EoE. However, could this cohort of asymptomatic EE be a precursor for future EoE cases? Likewise, is it possible that EE is an additional inflammatory burden and so it increases the disease activity of CD. These are ideas for future studies.

References

1. Liacouras CA, Furuta GT, Hirano I, Atkins D. Eosinophilic esophagitis: updated consensus recommendations for children and adults. J Allergy Clin Immunol. 2011; 128: 3-20.
2. Dellon E, Liacouras C, Molina-Infante J, Furuta GT. Updated International Consensus Diagnostic Criteria for Eosinophilic Esophagitis: Proceedings of the AGREE Conference. Gastroenterology. 2018; 155: 1022-1033.
3. Gupta SK, Fitzgerald JK, Kondratyuk T, Esch H. Cytokine expression in normal and inflamed esophageal mucosa: a study into the pathogenesis of allergic eosinophilic esophagitis. J Pediatr Gastroenterol Nutr. 2006; 42: 22-26.
4. Bullock JZ, Villanueva JM, Blanchard C, Filipovich AH. Interplay of adaptive Th2 immunity with eotaxin-3/c-C chemokine receptor 3 in eosinophilic esophagitis. J Pediatr Gastroenterol Nutr. 2007; 45: 22-31.
5. Liacouras CA, Spergel JM, Ruchelli E, Verma R. Eosinophilic esophagitis: a 10-year experience in 381 children. Clin Gastroenterol Hepatol. 2005; 3: 1198-1206.
6. Soon IS, Butzner JD, Kaplan GG, deBruyn JCC. Incidence and prevalence of eosinophilic esophagitis in children. J Pediatr Gastroenterol Nutr. 2013; 57: 72-80.
7. Cheifetz AS. Management of active Crohn disease. JAMA. 2013; 309: 2150-2158.
8. Neurath MF. IL-23: a master regulator in Crohn disease. Nature Medicine. 2007; 13: 26-28.
9. Molina-Infante J, Schoepfer AM, Lucendo AJ, Dellon ES. Eosinophilic esophagitis: What can we learn from Crohn's disease? United European Gastroenterol J. 2017; 5: 762-772.
10. Haberman Y, Tickle TL, Dexheimer PJ, Kim M-O. Pediatric Crohn disease patients exhibit specific ileal transcriptome and microbiome signature. J Clin Invest Am Soc Clin Investig. 2014; 124: 3617-3633.
11. Otley A, Loonen H, Parekh N, Corey M. Assessing activity of pediatric crohn's disease: Which index to use? Gastroenterology. 1999; 116: 527-553.
12. Levine A, Griffiths A, Markowitz J, Wilson DC. Pediatric modification of the Montreal classification for inflammatory bowel disease: The Paris Classification. Inflamm Bowel Dis. 2011; 17: 1314-1321.
13. Pensabene L, Brundler MA, Bank JM, Di Lorenzo C. Evaluation of mucosal eosinophils in the pediatric colon. Dig Dis Sci. 2005; 50: 221-229.
14. Talley N, Walker M, Aro P, Ronkainen J. Non-ulcer dyspepsia and duodenal eosinophilia: An Adult Endoscopic Population-Based Case Control Study. Clin Gastroenterol Hepatol. 2007; 5: 1175-1183.
15. Gunasekaran T, Prabhakar G, Schwartz A, Gorla K. Eosinophilic Esophagitis (EoE) in Children and Adolescents with Abdominal Pain: Comparison with EoE-Dysphagia and Functional Abdominal Pain. Can J Gastroenterol Hepatol. 2016.
16. Gunasekaran T, Chu C, Chennuri R, Adley B. Detailed histologic evaluation of eosinophilic esophagitis in Pediatric Patients Presenting with Dysphagia or Abdominal Pain and Comparison of the Histology between the Two groups. Can J Gastroenterol Hepatol. 2017.
17. Fan YC, Steele D, Kochar B. Increased Prevalence of esophageal eosinophilia in patients with Inflammatory Bowel Disease. Inflamm Intest Dis. 2018; 3: 180-186.
18. Limketkai BN, Shah SC, Hirano I, Bellaguarda E. Epidemiology and implications of concurrent diagnosis of eosinophilic esophagitis and IBD based on a prospective population based analysis. Gut. 2019; 68: 2152-2160.