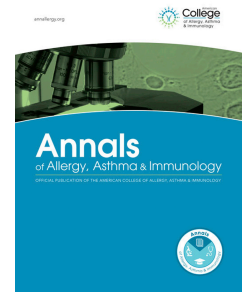


Accepted Manuscript

Concurrent Eosinophilic Esophagitis in pediatric patients with Inflammatory Bowel Disease – A case series

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PII: S1081-1206(19)30454-5

DOI: <https://doi.org/10.1016/j.anai.2019.06.010>

Reference: ANAI 2932

To appear in: *Annals of Allergy, Asthma and Immunology*

Received Date: 18 April 2019

Revised Date: 13 June 2019

Accepted Date: 17 June 2019

Please cite this article as: Talathi S, Knight T, Dimmitt R, Mestre J, Jester T, Concurrent Eosinophilic Esophagitis in pediatric patients with Inflammatory Bowel Disease – A case series, *Annals of Allergy, Asthma and Immunology* (2019), doi: <https://doi.org/10.1016/j.anai.2019.06.010>.

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TITLE PAGE

Title: Concurrent Eosinophilic Esophagitis in pediatric patients with Inflammatory Bowel Disease – A case series

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Funding Source: No funding was secured for this study.

Financial Disclosure: None of the authors of this manuscript have any financial relationships relevant to this article to disclose.

Word count: 1000

Number of figures: 0

Number of tables: 1

Conflict of Interest: The authors have no conflicts of interest to disclose.

Keywords: Eosinophilic esophagitis, EoE, IBD, inflammatory bowel disease, Crohn's disease, Ulcerative colitis

Coexistence of eosinophilic esophagitis (EoE) and inflammatory bowel disease (IBD) has recently been increasingly recognized, however, literature in pediatrics, especially in-depth characterization of these patient characteristics is scarce (1-3). This case series aims to describe the characteristics of 6 children with coexisting EoE and IBD at a single tertiary care center.

We performed a retrospective chart review all patients with coexisting EoE and IBD from the Pediatric IBD registry (350 patients followed since inception in 2014) at the University of Alabama at Birmingham/Children's of Alabama. Our pediatric IBD clinic follows children with IBD from all over the state of Alabama as well as neighboring states, thus representing the population demographics of the state of Alabama. Medical records were reviewed and patient demographics, information on symptoms, work up including histopathologic information and treatment was extracted. This study was approved by Institutional Review Board at University of Alabama.

Prevalence of EoE among our IBD population was 1.7% while that of IBD in our EoE population was 1.2%. Among the 6 patients with coexisting EoE and IBD, 5 (83%) were males and 5 (83%) were Caucasians. Mean age at diagnosis was 12 years (range 7.1 – 17.5 years) for EoE and 11 years (range 5 – 17.5 years) for IBD. Clinical features of our patient population are presented in Table 1. Symptoms of EoE included dysphagia (n=2), vomiting (n=2), retrosternal chest pain (n=1) and abdominal pain (n=5). History of atopic disease was present in 2 patients and peripheral eosinophilia was present in 3 patients. Four patients had Crohn Disease (CD) whereas 2 had Ulcerative Colitis (UC). Symptoms of IBD included chronic lower abdominal pain (n=6), diarrhea (n=6), and weight loss (n=4). Five patients had inflammatory markers drawn at presentation, and 4 had elevated erythrocyte sedimentation rate (ESR) and/or C-reactive

protein (CRP) levels. A fecal calprotectin level was obtained at presentation in only two patients and was elevated in both the patients.

The endoscopic and histologic findings of the 6 patients are summarized in Table 1. Characteristic endoscopic findings suggestive of EoE included longitudinal furrowing (n=2) and mucosal edema/inflammation (n=2). Histologic findings suggestive of EoE were as mentioned in consensus guidelines by Liacouras et al (4). None of the patients had esophageal narrowing on endoscopy. Endoscopic findings of IBD ranged from normal endoscopic appearance to evidence of pancolitis.

Four out of six (67%) patients were eventually treated with a biologic for their IBD, all four requiring anti-TNF alpha inhibitors (3 on infliximab and 1 on adalimumab). Patient on adalimumab was eventually transitioned to infliximab due to development of antibodies to adalimumab. One patient on infliximab required colectomy due to eventual lack of response and was then switched to an $\alpha 4\beta 7$ integrin blocker (vedolizumab). Patients not treated with biologics were on sulfasalazine (n=1) and azathioprine (n=1). With respect to EoE, 5 patients received viscous oral budesonide whereas one received high dose proton pump inhibitor. These patients improved symptomatically after initiation of treatment and repeat upper endoscopy in these patients showed improvement in histopathologic findings.

Consistent with recently published reports, the prevalence of EoE among our IBD population was higher than that in general population (3). These findings emphasize a possible but understudied association between these two conditions. Literature on coexistence of these two conditions in pediatric population, especially in-depth characterization is limited (3). Understanding the characteristics, natural course, response to treatment of this unique population with help in improved diagnostics and therapeutics for both the conditions.

IBD and EoE are chronic inflammatory conditions associated with dysregulated mucosal immune response, however, the type of immune response involved is different. EoE is thought to be an antigen mediated allergic condition in genetically predisposed individuals mediated by Th2 cells, leading to migration of eosinophils to the esophageal mucosa, their activation leading to secretion of proinflammatory mediators which causes an inflammatory response, muscular contractions and fibrosis resulting in esophageal dysfunction (4, 5). On the contrary, IBD is considered to be multifactorial in etiology with genetic susceptibility, environmental triggers, gut microbiome and immune responses interacting with each other to give different phenotypes of IBD (6).

Despite these differences, there are certain similarities in these two conditions which need to be emphasized. Firstly, both conditions have demonstrated genetic predisposition as evidenced of familial clustering and genetic variations (7, 8). Secondly, both the conditions have increased risk of developing other autoimmune conditions, including celiac disease, hypothyroidism, type I diabetes mellitus, asthma, and sarcoidosis (7, 9). Other similarities pertain to their increasing rates of incidence, natural history, effect on quality of life and possible utility of dietary therapy for treatment (10). It is suggested that these two conditions represent a spectrum of immune-mediated disease since there seems to be an overlap in immune mechanisms among the two, like overexpression of interleukin 13 (1).

Eosinophilia in the gastrointestinal tract is common in IBD and the number of eosinophils is dependent on the disease activity (11). Hence, the presence of active IBD (especially CD) needs to be considered in any patient with increased eosinophils in the esophagus and a history of IBD. Moreover, esophageal eosinophilia in IBD could also be due to reflux or concomitant EoE. Recent studies report that patients with coexistent IBD and EoE have a more complicated

course including IBD-related complications, poor response to infliximab and worse nutritional outcomes (2). Given these differences in natural course and treatment options, it is important to determine the cause of esophageal eosinophilia in IBD. Upper endoscopies in all our patients demonstrated characteristic findings diagnostic of EoE, suggesting a coexistence of both EoE and IBD.

This report emphasizes that the possibility of concurrent EoE and IBD needs to be considered by physicians, especially when eosinophilia in IBD patients is isolated to the esophagus and in presence of other histologic features of EoE. This will help in early diagnosis and appropriate treatment of these patients and also in better understanding of the interactions between these two conditions. Further larger studies need to be conducted to determine the association between these two conditions.

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Table 1: Characteristics of patients with coexisting IBD and EoE

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
Demographics						
Gender	Male	Male	Male	Male	Male	Female
Ethnicity	AA	Caucasian	Caucasian	Caucasian	Caucasian	Caucasian
Characteristics of IBD						
Age at diagnosis (years)	6.4	11.9	11.8	5	15.4	17.5
IBD phenotype	CD	CD	UC	CD	CD	UC
Presenting Symptoms						
• Diarrhea	Yes	Yes	Yes	Yes	Yes	Yes
• Hematochezia	No	No	Yes			Yes
• Abdominal pain	Yes	Yes	Yes	Yes	Yes	Yes
• Weight loss	Yes	No	Yes	Yes	No	Yes
• Extra-intestinal	Arthritis*	No	No	Arthritis	No	No
Laboratory markers						
• Hemoglobin (g/dL)	9.7 ⁺	12.4	12.7	n/a	11.4	8.9 ⁺
• ESR (normal < 15mm/h)	86	12	9	n/a	33	19
• Fecal calprotectin (normal <160 mcg/g)	448	n/a	>2000	n/a	n/a	n/a
Imaging*	Normal	Normal	N/A	Normal	Inflammation in the colon and small bowel thickening	Normal
Endoscopy at IBD diagnosis						
• Esophagus	Normal	Furrows	Normal	Normal	Furrows	Normal
• Stomach	Erythema	Antral nodules	Normal	Normal	Normal	Normal
• Duodenum	Erythema	Normal	Normal	Normal	Normal	Normal
• Terminal ileum	Erythema	Erythema, stricture	Normal	Normal	Normal	Normal
• Colon	Erythematous sigmoid	Erythema (except cecum)	Erythematous colon	Normal	Erythema, friability throughout colon	Erythema, friability (left sided)
Histology						
• Esophagus	Eosinophilic	EoE (see below)	EoE (see below)	Eosinophilic	EoE (see below)	EoE (see below)

• Stomach	infiltrate Neutrophilic cryptitis and abscess	Increased cellularity	Neutrophilic gastritis	infiltrate Normal	Neutrophilic gastritis	Increased cellularity
• Duodenum	Neutrophilic cryptitis	Normal	Normal	Normal	Neutrophilic duodenitis	Normal
• Terminal ileum	Neutrophilic cryptitis and abscess	Normal	Normal	Normal	Normal	Normal
• Colon	Normal	Neutrophilic cryptitis and abscess	Increased cellularity throughout the colon	Neutrophilic cryptitis, abscesses and fibrinopurulent exudate throughout the colon	Neutrophilic cryptitis, abscesses and fibrinopurulent exudate throughout the colon	Diffuse active chronic colitis (crypt distortion, abscess, ulceration and inflammation) – left sided
Treatment for IBD	Adalimumab**	Infliximab***	Azathioprine	Infliximab	Sulfasalazine	Infliximab
Characteristics of EoE						
Age at diagnosis (years)	7.1	11.9	11.8	9.3	15.4	17.5
Presenting Symptoms	Dysphagia, abdominal pain	Dysphagia, abdominal pain	Abdominal pain	Vomiting, abdominal pain	Chest pain	Vomiting, abdominal pain
Esophageal endoscopy findings at diagnosis of EoE	Edema, white plaques	Furrowing	None	Edema, inflammation	Furrows	None
Histology at diagnosis of EoE						
• Peak eosinophil count	100	30	45	15	24	25
• Basilar hyperplasia	Yes	Yes	Yes	Yes	No	Yes
• Elevated lamina propria	Yes	Yes	Yes	Yes	No	Yes
• Microabscess	Yes	No	No	No	No	No
• Fibrosis	Yes	Yes	No	No	No	No
Treatment for EoE	Oral budesonide slurry	Oral budesonide slurry	Oral budesonide slurry	Oral budesonide slurry	High dose omeprazole	Oral budesonide slurry

Note:

AA: African American; IBD: inflammatory bowel disease; CD: Crohn's disease; UC: Ulcerative colitis; ESR: Erythrocyte sedimentation rate; CRP: C-Reactive Protein;

*: Patient had a history of Juvenile idiopathic arthritis

**: Patient switched to infliximab

***Patient switched to vedolizumab after colectomy

[†]: indicates anemia for age and gender
