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High Prevalence of Eosinophilic Gastrointestinal Disease in Children with Intestinal Failure

Danielle Stamm, MSN, FNP[1,2], **Elizabeth Hait, MD, MPH**[3], **Heather J. Litman, PhD**[3,4], **Paul D Mitchell, MS**[4], and **Christopher Duggan, MD, MPH**[1,3]

[1]Center for Advanced Intestinal Rehabilitation, Boston Children's Hospital (BCH), Boston, MA

[2]Department of Surgery, Boston Children's Hospital (BCH), Boston, MA

[3]Division of Gastroenterology, Hepatology and Nutrition, Boston Children's Hospital (BCH), Boston, MA

[4]Clinical Research Center, Boston Children's Hospital (BCH), Boston, MA

Abstract

Objectives—To describe the prevalence and clinical features of gastrointestinal eosinophilic inflammation among pediatric patients with intestinal failure (IF).

Methods—Medical records of all patients followed in our institution's intestinal failure program who underwent GI endoscopy over a 15 year period were reviewed and clinical, pathologic, nutrition and laboratory data collected.

Results—One hundred and five patients underwent 208 GI endoscopic procedures with biopsy. The overall prevalence of eosinophilic inflammation, defined as increased eosinophils in at least one tissue type on at least one endoscopy, was 39/105 (37%). The tissue-specific prevalence of eosinophilic inflammation ranged widely, with the colon/rectosigmoid being the most common (18/68, 26%), followed by the esophagus (17/83, 20%), ileum (9/54, 17%), duodenum (4/83, 5%), and stomach (3/83, 4%). Higher peripheral eosinophil count and hematochezia were associated with eosinophilic inflammation in the colon (p=0.002 and 0.0004, respectively). The use of a strict elemental diet for 3 months prior to endoscopy was not associated with a decreased frequency of eosinophilic inflammation in any tissue.

Conclusions—Eosinophilic inflammation is a common histopathologic finding in IF patients. Colonic eosinophilic inflammation is associated with clinical symptoms of GI blood loss, and peripheral eosinophilia, and was not abrogated by a strict elemental diet.

Corresponding author: Christopher Duggan, MD, MPH, Address: Center for Nutrition, Division of Gastroenterology, Hepatology and Nutrition, Boston Children's Hospital, 333 Longwood Avenue, Boston, MA 02115. Phone: +1 617-355-7612, Fax: 617-730-0477, christopher.duggan@childrens.harvard.edu.

Author Contributions: Danielle Stamm, MSN, FNP: study design, chart review, data collection, developed first draft of manuscript

Elizabeth Hait, MD, MPH: study design, chart review, data collection, contributed to manuscript

Heather Litman, PhD: statistical analysis, contributed to manuscript

Paul Mitchell, MS: statistical analysis, contributed to manuscript

Christopher Duggan, MD, MPH: study design, chart review, data collection, contributed to manuscript

Keywords

short bowel syndrome; colitis; esophagitis; hematochezia; allergy; intestinal failure

Introduction

Intestinal failure (IF) is characterized by an inability to absorb adequate nutrients through the gastrointestinal (GI) tract due to insufficient bowel length and/or function. Although there are numerous underlying causes of pediatric IF (including gastroschisis, intestinal atresias, necrotizing enterocolitis, and others), successful intestinal rehabilitation in this population is universally designed to foster increased tolerance of enteral nutrition (EN), while decreasing or eliminating the need for parenteral nutrition (PN). Due to the significant complications associated with long term PN, aggressive advancement of enteral feeding is a mainstay of treatment (1-4). Improved understanding of potential barriers to advancing EN is integral to optimizing management and improving outcomes.

GI inflammation has been observed in pediatric IF, and may represent one such barrier. Inflammation has been shown to correlate with PN dependence, and may be related to common comorbidities of IF such as bowel ischemia and/or small bowel bacterial overgrowth (5). We have previously demonstrated that pediatric IF patients undergoing GI endoscopy have high rates of gross endoscopic, histologic or microbiologic findings, with 89% of patients in a recent cohort showing some abnormality and 15% having histopathologic evidence of allergic inflammation (6).

Limited data describe GI eosinophilic inflammation in IF. Taylor et al. reported a case series of pediatric IF patients with hematochezia and eosinophilic colitis that was temporally associated with enteral feeding advancement. They noted improvement in bloody stools with bowel rest and, in some cases, treatment with sulfasalazine (7). Eosinophilic gastrointestinal disease was also reported in 2 children with long-segment Hirschsprung's disease related to Shah-Waardenburg syndrome (8). Another study reported the incidental finding of eosinophilic inflammation in the rectum of 17% of children being evaluated for Hirschsprung's disease. Of this group, 48% were diagnosed with a food and/or milk allergy at follow up, suggesting that this finding may indicate underlying pathology (9). Finally, an association between IF and cow's milk allergy has been proposed. Three infants with IF and feeding intolerance when given intact milk protein-based formula all had positive specific IgE for cow's milk proteins. Improved feeding tolerance was reported when they were transitioned to a hydrolyzed or elemental formula (10).

Since the literature concerning the occurrence of gastrointestinal eosinophilic inflammation in IF is generally limited to small case series, we sought to determine the prevalence of this condition in a large cohort of pediatric IF patients, and also aimed to identify risk factors for its occurrence.

Methods

Following approval by our institutional review board, the medical records of all patients who underwent gastrointestinal endoscopy over a 15-year period (1997-2012) and who attended our multidisciplinary program in pediatric intestinal rehabilitation (11) were reviewed. Histopathologic, laboratory, and nutritional data were collected.

Indications for endoscopy were varied and were not mutually exclusive. These included diarrhea, hematochezia, hemoccult positive stools, and/or emesis. In the small bowel and colon, the extent of eosinophils was ranked as mild, moderate or severe, and the depth of tissue involvement (superficial, lamina propria) was reported. In the esophagus and stomach, histopathologic findings were classified as eosinophils per high power field (eos/hpf) in the following groups; scattered (<10/hpf), and 10-100 eos/hpf. Data from all endoscopic reports were collected by a single gastroenterologist (EH).

Nutrition exposures were recorded for the 3 months preceding endoscopy, and were categorized by use of PN, amino acid-based formula, protein hydrolysate formula, intact protein formula, and/or solid foods. Interpretation of laboratory data was in accordance with the Boston Children's Hospital (BCH) normative ranges. Patients were considered to have bacterial overgrowth if cultures of fluid aspirated from the duodenum grew $\geq 10^5$ colonies of any organism (12). Subjects were defined as having atopic disease if they had any of the following: atopic dermatitis, allergic rhinitis, food allergies, reactive airway disease or seasonal allergies.

Statistical analysis was performed to assess for predictors of eosinophils on endoscopy both within and across tissue types. This manuscript describes patients with intestinal failure undergoing repeated endoscopies. Baseline characteristics are presented as n (%) or median (IQR). Comparison of selected factors between subjects with and without eosinophilic inflammation were conducted; Wilcoxon rank-sum tests were used to compare continuous variables, and Pearson Chi-squared or Fisher's exact tests were used to compare categorical variables, the latter used when any expected cell count was <5. A general estimating equation (GEE) with an empirical sandwich estimator was used to investigate characteristics associated with presence of eosinophilic inflammation, after adjusting for correlation due to repeated endoscopies within subjects (13). All tests of significance were two-sided and $P<0.05$ used as a threshold for statistical significance.

Results

A total of 208 GI endoscopies with biopsy were performed on 105 patients during the 15-year study period. The median (interquartile range) number of endoscopies per patient was 1 (1, 2). Patient demographics are summarized in Table 1. The majority of patients (59%) were PN dependent during the 3 months prior to their first endoscopy and the median minimum citrulline concentration was 14 micromol/L, suggesting significant ongoing intestinal failure in a large percentage of patients (14).

Eosinophilic inflammation was a frequent finding in this cohort, with 39/105 (37%) of subjects having increased eosinophils in at least one tissue type on at least one endoscopy.

The tissue-specific prevalence of eosinophilic inflammation ranged widely, with the colon/rectosigmoid being the most common site (18/68 subjects, 26%), followed by the esophagus (17/83, 20%), ileum (9/54, 17%), duodenum (4/83, 5%), and stomach (3/83, 4%).

Esophageal biopsy results were positive for eosinophils in a total of 24 endoscopies (n = 17 subjects): 12 showed scattered eosinophils, 11 showed >10 eos/hpf, and one was unquantified. Gastric biopsy results were positive for eosinophils in three endoscopies (n = 3 subjects): two showed scattered eosinophils and one was unquantified. Small bowel biopsy results were positive for eosinophils in 13 endoscopies (n = 13 subjects): ten were mildly increased, two were moderately increased and one was severely increased. Two were superficial in depth, two did not specify and 9 extended to the lamina propria. Colonic biopsy results were positive for eosinophils in 18 lower endoscopies (n=18 subjects): 8 were mildly increased, 9 were moderately increased and one was severely increased. The depth of colonic eosinophilic inflammation reached the lamina propria in all 18 cases.

Factors associated with the finding of eosinophilic inflammation on initial endoscopy (n=105) are detailed in Table 2. Underlying etiology of intestinal failure was not related to the presence of eosinophilic GI inflammation, nor was gestational age or sex. Nutritional intake (including PN dependence, use of elemental diet, or use of solid foods/intact protein formula during the 3 months prior to endoscopy) was also not related to the presence of eosinophilic inflammation on initial endoscopy. Factors associated with eosinophilic inflammation were hematochezia ($p = 0.01$) and peripheral eosinophil count ($p = 0.0009$).

Since the finding of eosinophilic inflammation was most prevalent in the esophagus and colon, these tissue types were of particular interest. Tables 3 and 4 include analyses of nutrition risk factors for eosinophilic inflammation in these tissue types across all endoscopies. In the esophagus, dietary solid food intake was associated with a significant increase in prevalence of eosinophilic inflammation ($p = 0.02$). However, in the colon, dietary solid food intake was associated with a significant decrease in prevalence of eosinophilic inflammation ($p = 0.02$). Finally, those with intake of intact-protein formula (in the absence of solid foods) were more likely to have eosinophilic inflammation in the colon ($p = 0.02$). These dietary associations were not observed in analyses restricted to the initial endoscopy across all tissue types. PN dependence was not significantly associated with eosinophilic inflammation in any tissue. The significant association of peripheral eosinophil count and hematochezia with eosinophilic inflammation observed for combined tissue types for initial scope-only was also observed when assessing the colon separately across all scope events ($p=0.002$ for peripheral eosinophil count and 0.0004 for hematochezia).

Discussion

Patients with intestinal failure are dependent on long-term specialized nutrition due to reduced absorptive function from congenital or acquired lesions of the bowel. In this large, retrospective review, we have demonstrated that gastrointestinal eosinophilic inflammation is a common concomitant finding in these patients, affecting nearly 40% of subjects and multiple regions of the GI tract. Correlation of eosinophilic inflammation in the colon with

hematochezia and higher peripheral eosinophil counts suggests that these findings on histopathology may have clinical significance.

Others have postulated that children with intestinal failure may be more susceptible to dietary protein allergy, but few large or rigorous studies have been performed (15, 16). One potential triggering mechanism to allergic gastrointestinal disease in IF is increased intestinal permeability (17). Although animal studies have not consistently demonstrated increased mucosal permeability in IF models, clinical studies have supported this relationship (18-20). Furthermore, elemental diets have also been associated with improved outcomes in infants with IF in multiple small case series, suggesting that intestinal adaptation might be enhanced by diets low in intact protein antigens (21, 22).

Our finding that adherence to a strict elemental diet did not consistently abrogate the risk of GI eosinophilic inflammation was of interest, particularly in the group with eosinophilic colitis. These patients frequently had concomitant elevation in peripheral eosinophil count and/or hematochezia prompting clinical concern and need for effective therapeutic interventions. Although it is possible that an elemental diet may be helpful in managing symptomatic eosinophilic colitis, the findings of the present study suggest that this approach may not be definitive. These results also beg the question of the mechanism by which this histologic finding in intestinal failure patients occurs.

Our effort to identify possible risk factors for eosinophilic inflammation and, more specifically, eosinophilic colitis, yielded relatively few positive correlations between numerous clinical, demographic and nutritional factors, and the occurrence of eosinophilic inflammation. The positive association between intake of a more varied diet (dietary solids) and eosinophilic inflammation in the esophagus specifically (along with a trend toward a strict elemental diet as being protective in this tissue type) is consistent with current literature regarding dietary treatment of eosinophilic esophagitis (23). Findings in the colon of our group of patients were more difficult to interpret, in that intact protein formula was associated with an increased risk for eosinophilic colitis whereas dietary solids were associated with a decreased risk. These findings, along with the fact that no dietary risk factors were positively associated with eosinophilic inflammation when analyzing initial endoscopy only across all tissue types, suggest that nutritional exposures alone do not seem to trigger nor prevent this endoscopic finding. The absence of any clear risk factor for the occurrence of GI eosinophilic inflammation in this large patient cohort suggests that the etiology may be multi-factorial and warrants future study.

Strengths of the present study include its relatively large sample size, single center location and extensive investigation of possible risk factors for eosinophilic inflammation. Limitations include the semi-quantitative classification of eosinophilic inflammation. It is fairly well accepted that normal esophageal mucosa does not contain eosinophils, however all other types of GI mucosa likely have a baseline level of eosinophils whose frequency and function is yet to be clearly defined (24). The designation of “increased” eosinophils in this study is therefore inherently subjective and relies on the experience of the GI pathologist to distinguish levels of eosinophils that exceed the norm. Regardless of this evolving body of knowledge, the notion that eosinophils are found in increased numbers in the setting of

inflammation is widely accepted, and recent studies have associated increased numbers of gastrointestinal eosinophils with a variety of specific inflammatory GI diseases (25, 26). Another limitation of this work, as with many retrospective studies, was our inability to provide adequate follow up data to definitively analyze outcomes of treatment modalities used in patients with eosinophilic inflammation. Likewise, its cross-sectional nature did not allow us to evaluate whether a causal relationship exists between the presence of eosinophilic inflammation and the degree of PN dependence, although our findings of a high prevalence of tissue inflammation in an IF cohort suggest that this relationship bears further investigation.

In summary, we found a high prevalence of gastrointestinal eosinophilic inflammation in a large cohort of children with intestinal failure. The medical and nutritional care of these patients should include an awareness of this common endoscopic finding, and careful screening for symptoms such as hematochezia, which warrant evaluation and intervention.

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Textbox

- Previous case series describe a non-infectious, eosinophilic colitis in infants with IF, suggesting this may be a common finding in pediatric IF.
- GI inflammation has been shown to correlate with PN dependence in pediatric IF.
- In this large cohort of pediatric IF patients, 37% had evidence of eosinophilic inflammation on at least one endoscopy, most commonly in the colon.
- Adherence to a strict elemental diet was not associated with a lower incidence of eosinophilic inflammation.
- Elevated peripheral eosinophil counts and hematochezia were each significantly associated with eosinophilic inflammation in the colon.

Table 1

Baseline characteristics in 105 children with intestinal failure who underwent gastrointestinal endoscopy

Characteristic	N (%) or Median (IQR)
Male sex	56 (53%)
Age at first endoscopy (years)	2.7 (1.1, 5.8)
Gestational age <37 weeks (n=92)	69 (75%)
Caucasian race	64 (61%)
Primary Diagnosis *	
Necrotizing enterocolitis (NEC)	35 (33%)
Gastroschisis	22 (21%)
Volvulus	20 (19%)
Hirschsprung's disease	9 (9%)
Ileal atresia	9 (9%)
Jejunal atresia	8 (8%)
Chronic intestinal pseudo-obstruction	7 (7%)
Cloacal exstrophy	5 (5%)
Microvillus inclusion disease	1 (1%)
Other	13 (12%)
History of atopic disease	57 (54%)
Minimum serum citrulline (micromol/L) (n=50)	14 (9, 21)
PN dependent **	62 (59%)

* Not mutually exclusive

** Within 3 months prior to procedure

Table 2

Association of select factors with eosinophilic inflammation in any tissue on initial endoscopy in 105 children with intestinal failure

	Eosinophilic Inflammation		
	No (n=74)	**Yes (n=31)**	**P value****
Demographics			
Male Sex	39 (53%)	17 (55%)	0.84
Gestational Age <37 weeks (n=92)	49 (75%)	20 (74%)	0.89
Diagnosis*			
Necrotizing enterocolitis	24 (32%)	11 (35%)	0.76
Gastroschisis	19 (26%)	3 (10%)	0.07
Ileal atresia	5 (7%)	4 (13%)	0.44
Jejunal atresia	4 (5%)	4 (13%)	0.23
Volvulus	11 (15%)	9 (29%)	0.09
Pseudo-obstruction	6 (8%)	1 (3%)	0.67
Hirschsprung's Disease	9 (12%)	0 (0%)	0.06
Nutrition			
Amino acid-based formula	15 (20%)	9 (29%)	0.33
Intact protein formula	9 (12%)	5 (16%)	0.55
Intact protein formula + solids	50 (68%)	21 (68%)	0.99
PN	43 (58%)	19 (61%)	0.76
Labs			
Peripheral absolute eosinophil count (median, IQR) (n=83)	0.26 (0.15, 0.49)	0.66 (0.41, 1.45)	0.0009
Other			
Hematochezia	8 (11%)	10 (32%)	0.01
Duodenal aspirates collected	22 (30%)	6 (19%)	0.27
Small bowel bacterial overgrowth (n=15 among patients with duodenal aspirates collected)	12 (55%)	3 (50%)	1.00
Atopic disease	41 (55%)	16 (52%)	0.72

*Not mutually exclusive

**Fisher exact, chi square or Wilcoxon rank sum test

Table 3

Nutritional Factors and Eosinophilic Inflammation in 136 Upper GI Endoscopies with Esophageal Biopsy

Characteristic	EOS+ (n=24)	EOS- (n=112)	P Value*
Strict amino acid-based diet	2 (8%)	28 (25%)	0.09
Protein hydrolysate formula	5 (21%)	16 (14%)	0.47
Intact protein formula	2 (8%)	11 (10%)	0.86
Dietary solids	22 (92%)	72 (64%)	0.02

*General estimating equation

Table 4

Nutritional Factors and Eosinophilic Inflammation in 101 Colonoscopies with Colonic/ Rectosigmoid Biopsy

Characteristic	EOS+ (n=21)	EOS- (n=80)	P value*
Amino acid-based formula	8 (38%)	18 (23%)	0.15
Protein hydrolysate formula	2 (10%)	8 (10%)	0.95
Intact protein formula	5 (24%)	4 (5%)	0.02
Dietary solids	9 (43%)	55 (69%)	0.02

*General estimating equation