



Pediatric Duodenal Mucosal Biopsies with Eosinophilic Infiltrates: A Clinicopathologic Study

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Authors' contributions

This work was carried out in collaboration between all authors. Author MSM designed the study, wrote the protocol and the first draft of the manuscript. Authors LAD and MF reviewed all biopsy slides and helped in designing the study and writing the manuscript. Authors SHA, WJK and MAG helped in designing the study, reviewing the data, literature review and writing the manuscript. All authors read and approved the final manuscript.

Short Communication

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ABSTRACT

Aims: To describe the clinicopathologic features of children with Duodenal eosinophilic infiltrates (DEI).

Study Design: Retrospective.

Place and Duration of Study: Pediatric Gastroenterology Division, Texas Children's Hospital over 24 months (Jan 1, 1998 –Dec 31, 1999).

Methodology: Children with DEI at Texas Children's Hospital over 24 months were identified. Clinical symptomatology was analyzed by a retrospective medical record review. Two pediatric pathologists re-evaluated all biopsies. Follow-up was done by contacting the patients 12-36 months after the initial diagnosis.

Results: Total number of GI biopsies that included duodenum over the study period was 1145 biopsies. Out of 1145 cases, 780(68%) cases indicated eosinophilic infiltrates (EI) at some GI site. Out of these, 287(37%) cases had DEI. Mean age was 10.4 years. (F: M .2:1). Race: 197(79%) Caucasians, 37(15%) Latin Americans, 9(4%) African Americans and 6(2%) Arabs. Clinical symptomatology: 249 records were available for

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evaluation. 69.9% complained of abdominal pain, 55% had vomiting, 34.9% with diarrhea and 32.9% had weight loss. 105 patients were available for follow up; 38% continued to have abdominal pain, 15.2% with vomiting, 10.5% diarrhea and 7.6% had a persistent weight loss. Peripheral eosinophilia was present in 35.2%. Medical treatment included proton pump inhibitors (57.0%), H2-blockers (55.4%), steroids (26.5%), and elemental diet (9.6%). Histopathology: 6% had <10 eosinophils /hpf, 51.8% with 10-20eos/hpf, and 42.2% with >20 eos/hpf. There were no significant differences in the number of eos/hpf between those with or without a specific symptom. Fourteen children (5.6%) subsequently developed IBD; their histopathological data did not differ from the rest.

Conclusion: 1) children with DEI present with variable chronic symptoms 2) symptoms persisted in a significant number of patients despite therapy, 3) Close observation is warranted since a small number of patients may develop IBD.

Keywords: Eosinophils; duodenum; gastrointestinal; mucosa; eosinophilia and endoscopy.

1. INTRODUCTION

The eosinophil is a non-specific, late-phase inflammatory cell appearing in the intestinal mucosa under several acute and chronic inflammatory conditions, such as infections, drug-reactions, celiac disease, intestinal allergies, Crohn's disease, etc. In addition, the mucosa of the intestine harbors activated eosinophils even under resting conditions. The threshold eosinophil level discriminating resting from inflammatory conditions is so far not clearly defined.

Eosinophilic esophagitis (EoE) is an inflammatory disease of the esophagus that is being increasingly reported in children and adults [1,2]. The etiology is poorly understood. Food or aeroallergen hypersensitivity is involved in about 50% of cases of EoE. Children with EoE have a variety of symptoms including abdominal pain, nausea, vomiting, regurgitation, dysphagia, heartburn and failure to thrive [2,3,4]. Recognition of increased eosinophils in gastrointestinal (GI) mucosal biopsies also appears to be increasing, but little data is available to support this contention. Duodenal eosinophilic infiltrates (DEI) in particular appear to be a more common finding in children undergoing endoscopy for various gastrointestinal complaints [2].

The number of eosinophils and the clinical significance of DEI remain controversial. Such diagnoses are entirely descriptive and operator-dependent because standards for an acceptable number of eosinophils in asymptomatic children are few [2].

The aim of our study is to describe the clinicopathologic features of children with DEI. We hypothesize that the prevalence of duodenal mucosal biopsies with increased eosinophils is high among patients with GI complaints & the presence of increased eosinophils in duodenal mucosal biopsies is related to specific symptoms.

Provide a factual background, clearly defined problem, proposed solution, a brief literature survey and the scope and justification of the work done.

2. MATERIALS AND METHODS

The surgical pathology database at Texas Children's Hospital in Houston, Texas, USA was searched for gastrointestinal (GI) biopsies that included duodenal biopsies over a period of two years (from January 1, 1998 to December 31, 1999). GI biopsies in which the pathology report indicated increased eosinophils at some gastrointestinal site were identified using an electronic search that included the words: eosinophilia, eosinophilic, with eosinophils, increased eosinophils, and eosinophilic infiltrate. Out of all the GI biopsies with increased eosinophils, cases with duodenal mucosal eosinophilia were selected for further evaluation.

We analyzed the clinical, laboratory and histopathological data of the selected cases. The clinical symptomatology was analyzed by a retrospective medical record review. To identify current symptoms (i.e. follow up status), patients were contacted by phone 12-36 months after the time of initial diagnosis. Patients were asked about current gastrointestinal symptoms, diet modification, and current medications to control their symptoms, new medical conditions, and the use of alternative medicine. Laboratory data was obtained from the medical record and electronic lab database. The histopathological data was obtained by re-examining all the biopsies by two pediatric pathologists who was blinded to clinical data. The maximum number of intramucosal eosinophils was counted in ten consecutive high power fields (HPF; 400X) in the duodenum and other available gastrointestinal biopsies.

3. RESULTS

The total number of gastrointestinal biopsies that included duodenal biopsies done over the study period (from January 1, 1998 and December 31, 1999) was 1145 biopsies. Eosinophilic infiltrates as identified in the electronic pathology report (Fig.1) at some gastrointestinal site were identified in 780 cases (68%). Out of these, 287 (37%) cases had duodenal eosinophilic infiltrates (DEI). Cases were excluded if the medical record or biopsy were not available. Two hundred forty-nine biopsies and medical records were available for review out of the 287 biopsies carrying the diagnosis of DEI (87%). The age range was between 1 year and 18 years, with a mean age of 10 years and 5 months. Female to male ratio was 1.2:1. Race and ethnicity of subjects included: 197(79%) Caucasians, 37 (15%) Latin Americans, 9(4%) African Americans and six (2%) Arabs.

Clinical Data: Clinical symptomatology is described in Table 1. Abdominal pain was the most frequent complaint in 174 patients (69.9%), followed by vomiting in 137 patients (55.0%). One hundred seventy one patients (68.7%) had two or more symptoms, 129 patients (51.8%) had three or more symptoms. Abdominal pain and vomiting was the most frequent combination of symptoms (97 patients, 38.9%). All symptoms were more common in females, except for reflux symptoms and diarrhea, which were more common in males. Allergic non- gastrointestinal symptoms were found in a significant number of patients. A personal history of asthma was found in 53 children (21.3%), history of allergies (other than asthma) was found in 85 (34.1%) children. Some children (39 patients, 15.7%) have both asthma and other allergies. There was no statistically significant association between asthma with any particular GI symptoms. A family history of allergies was common; noted in 93 (37.3%) children. Arthralgia was reported in only nine patients (5 M: 4 F), (3.6%).

Treatment modalities varied significantly, mainly depending on the treating physician. The most frequent class of medications used was proton pump inhibitors (PPI) (57.0%) followed by H2 blockers (55.4%). Systemic steroids were used in more than a quarter (26.5%) of the

patients. Steroid dosing ranged from 0.5 to 3 mg/kg/day (average: 1 mg/kg/day). The duration of steroid treatment ranged from 1 week to 2 months (average: 25 days). Some form of dietary modification was suggested for 61 patients (24.5%), 24 of them (9.6%) were placed on elemental diet. Details of different treatment modalities used are shown in Table 2.

Table 1. Clinical symptomatology in patients with DEI (n=249)

Clinical Symptom	Total Number (%)	Males	Females
Abdominal Pain	174 (69.9)	73	101
Vomiting	137 (55.0)	62	75
Reflux symptoms	124 (49.8)	72	52
Nausea	91 (36.5)	34	57
Decreased appetite	89 (35.7)	42	47
Diarrhea	87 (34.9)	47	40
Weight loss	82 (32.9)	40	42
Blood in the stool	44 (17.7)	21	23
FTT	36 (14.5)	18	18

DEI: Duodenal eosinophilic infiltrates

Table 2. Treatment modalities

Treatment modality	Number of patients (%)
PPI	142 (57.0)
H2 Blockers	138 (55.4%)
Systemic steroids	66 (26.5)
Diet modification	61(24.5%)
Elemental diet	24 (9.6%)
5ASA	15 (6.0)
Periactin	12 (4.8)
Megestrol Acetate	9 (3.6)

PPI: proton pump inhibitor

Laboratory Investigations: 142/249 children had a CBC with differential count done as part of their laboratory work- up. Peripheral eosinophilia, defined as > 5% of the total white blood cell count, was found in 50 children (35.2% of the patients having this work-up). The details are shown in Table 3. Stool giardia antigen testing was negative in all tested children (41 patients). RAST testing was performed in 31 patients (12.4%), and was positive in more than half of them (17 patients, 55%). Milk and eggs were the most commonly identified allergens (10/17 patients). Other allergies included peanuts, pork, beef, and soy. Celiac serology testing (anti-gliadin and anti-endomysial antibodies) was done in 13 children. Seven patients tested positive for anti-gliadin antibodies, and one patient for anti-endomysial antibodies. None of the patients had celiac disease by small intestinal biopsy.

Table 3. Peripheral eosinophilia

Percentage of eosinophils	Number of Patients (%)
5%- < 10%:	37 (74%)
> 10% - <20%:	11(22 %)
> 20%:	2 (4%)
Total	50 (35.2 % of the patients with CBC)

Histopathological Data: Two pediatric pathologists, blinded to clinical data, reviewed all gastrointestinal biopsies. In duodenal biopsies, a high percentage of the patients (42.2%) had > 20 eosinophils /high power (40X objective) field (eos/hpf). There were no statistically significant differences in the number of eos/hpf between those with or without a specific symptom. The details of the maximum number of eosinophils noted in the duodenum are shown in Table 4. In our patients with DEI, we studied all other available gastrointestinal biopsies.

Table 4. Maximum number of eosinophils noted in the duodenum

Max. No. of Eos	Number of Patients (%)
< 10 Eos/HPF	15(6.0)
10 – 20 Eos /HPF	129(51.8)
> 20 Eos /HPF	105(42.2)
Total	249 patients

Eos: eosinophils, HPF: high power field

Esophagus: One hundred and eight patients (43.4%) with DEI had esophageal biopsies. Most of these patients (63%) had no significant pathological changes, and eosinophilic infiltrate was noted in only 7/108 patients (6.5 %). Detailed description of the results is shown in Table 5.

Table 5. Esophageal biopsies in patients with DEI

Histological findings	Number of patients (%)
No pathological changes	68 (63.0)
Reflux	22 (20.4)
Eosinophilic infiltrate (>1/HPF)	7 (6.5)
Chronic inflammation	6 (5.6)
Acute inflammation	1(0.9)
Non-specific changes	4 (3.7)
Total	108

HPF: high power field

Stomach: One hundred and twenty-eight patients (51.4%) with DEI had stomach biopsies. Although most of these patients (60.9%) had no significant pathological changes, eosinophil density > 3/HPF was noted in 28/128 patients (21.9 %). Detailed results are shown in Table 6.

Table 6. Gastric biopsies in patients with DEI

Histological findings	Number of patients (%)
No pathological changes	78 (60.9)
Eosinophilic infiltrate (>3/HPF)	28 (21.9)
Acute inflammation	1 (0.8)
Chronic inflammation	15 (11.7)
Non-specific changes	6 (4.7)
Total	128

HPF: high power field

Colon: Fifty two patients (20.9%) with DEI had colon biopsies. Although most of these patients (65.4%) had no significant pathological changes, eosinophil density > 12/HPF was noted in 14/ 52 patients (26.9 %). Detailed results are shown in Table 7.

Table 7. Colonic biopsies in patients with DEI

Histological findings	Number of patients (%)
No pathological changes	34 (65.4)
Eosinophilic infiltrate (>12/ HPF)	14 (26.9)
Chronic inflammation	4 (7.7)
Acute inflammation	0 (0.0)
Total	52

DEI: Duodenal eosinophilic infiltrates, HPF: high power field

Follow up: One hundred and five patients (42.2%) (M: 45, F: 60) out of the 249 patients with the diagnosis of DEI were available for follow-up by telephone. The reasons for not being able to contact the rest of the patients included the following: incorrect contact information, disconnected telephone, the patient had moved and the new address was not available, or their was no response from the patients after three separate phone call attempts made at different times of the day and on different days of the week. The follow- up phone calls was made at 12-36 months after the time of initial diagnosis. Fifty-eight patients (55.2%) (26 males and 32 females; 44.8% and 55.2%, respectively) were free of any GI symptoms. Forty-seven patients (44.7%) (19 males and 28 females; 40.4% and 59.6%, respectively) continued to have at least one gastrointestinal complaint. Analysis of their persistent complaints revealed that the most frequent persistent complaint was abdominal pain (38.0%) followed by nausea (22.9%). On follow-up 20/105 patients (19.0%) were still on some form of diet modification. A striking percentage of patients (40.0%) were still on medications to control their gastrointestinal complaints. Only four patients admitted utilizing alternative medicine. Details of follow up clinical data are shown in Table 8.

Table 8. Follow up clinical features. (105 patients)

Clinical Symptom	Number of patients (%)
Follow up Meds	42 (40.0)
Abdominal Pain	40 (38.0)
Nausea	24 (22.9)
Diet modification	20 (19.0)
Vomiting	16 (15.2)
Diarrhea	11 (10.5)
FTT	8 (7.6)
Weight loss	8 (7.6)

FTT: failure to thrive

To better understand the persistence of specific symptoms, we further studied those patients who were available for follow-up. Their symptoms at the time of initial diagnosis were compared to their reported symptoms at the time of follow up. The symptoms that were most likely to persist were failure to thrive (57%), nausea (55%), and abdominal pain (44%). The symptom that was least likely to persist was weight loss (21%). It is interesting to know that most patients (20/23 patients: 87%) who were on diet modification at the time of initial diagnosis continued to utilize it at the time of follow up. Further details are shown in Table 9.

Table 9. Persistence of specific symptom at time of follow up in available patients (n=105)

Symptom	No. of patients at time of Diagnosis	No. of patients at time of follow up	% of patients with persistence of specific symptom
FTT	14	8	57%
Nausea	44	24	55%
Abdominal Pain	91	40	44%
Diarrhea	37	11	30%
Vomiting	55	16	29%
Weight loss	39	8	21%
Diet modification	23	20	87%

FTT: failure to thrive

Long-term prognosis: Fourteen children (5.6%) subsequently developed inflammatory bowel disease (IBD). Five patients (4 males, 1 female) developed Crohn's disease. Four children developed ulcerative colitis, (3 females, 1 male). Another five patients (2 males, 3 females) developed indeterminate colitis.

Those children who later developed IBD were studied further. The age range at time of diagnosis was between 4 years and 18 years, with a mean age of 13 years and 5 months.

Female to male ratio was 1:1. Almost all of them (12/14, 85.7%) were Caucasians; one child was Mexican American, and another child was of Arabic ancestry. Abdominal pain (13/14, 92.9%) and diarrhea (12/14, 85.7%) were the most frequent symptoms. Comparing the clinical symptomatology of these patients with the rest of the patients with DEI; they were more likely to have abdominal pain (92.9% vs. 69.9%), diarrhea (85.7% vs. 34.9%), and blood in the stool (57.1% vs. 17.7%) but less likely to have reflux (21.4% vs. 49.8%). It is difficult to conclude statistical significance giving the small number in the IBD group. Details are shown in Table 10.

Table 10. Clinical symptomatology of patients with DEI who developed inflammatory bowel disease (n=14) vs. all children with DEI (n=249)

Clinical Symptom	Patients who developed IBD: Total Number (%)	All children with DEI Total Number (%)
Abdominal Pain	13 (92.9)	174 (69.9)
Diarrhea	12 (85.7)	87 (34.9)
Blood in the stool	8 (57.1)	44 (17.7)
Vomiting	8 (57.1)	137 (55.0)
Nausea	7 (50.0)	91 (36.5)
Weight loss	5 (35.7)	82 (32.9)
Decreased appetite	4 (28.6)	89 (35.7)
Reflux	3 (21.4)	124 (49.8)
FTT	1 (7.1)	36 (14.5)
<i>Total</i>	14 patients	249 patients

DEI: Duodenal eosinophilic infiltrates. FTT: failure to thrive

The histopathological findings of these patients subsequently diagnosed on with IBD did not differ from the histopathological findings of the rest of the patients with DEI. The maximum

number of eosinophils noted in the duodenum was 30 eos/hpf (range 11-30 eos/hpf, average 21/HPF). None of them had eosinophilic infiltrate of the esophagus. One patient had eosinophilic infiltrate of the stomach and two had eosinophilic infiltrate of the colon. Details are shown in Table 11.

Table 11. Maximum number of eosinophils noted in the duodenum of patients with DEI who developed inflammatory bowel disease vs. all children with DEI

Max. No. of Eos	Patients who developed IBD: Total Number (%)	All children with EDI Total Number (%)
< 10 Eos/HPF	1 (7)	15(6.0)
10 – 20 Eos /HPF	8 (57)	129(51.8)
> 20 Eos /HPF	5 (36)	105(42.2)
Total	14 patients	249 patients

DEI: Duodenal eosinophilic infiltrates. Eos: eosinophils. HPF: high power field. FTT: failure to thrive

4. DISCUSSION

Our data suggest that most children undergoing upper endoscopy for evaluation of GI symptoms who have duodenal eosinophilic infiltrates have allergic history or symptoms. The finding of a high prevalence (68%) of eosinophilic infiltrates at some GI site or specific to the duodenum (37%) in this large sample size is noteworthy, but we did not identify symptoms specific to children with DEI. Of importance, a small number (5%) of children with DEI developed inflammatory bowel disease within three years.

DEI is not a distinct entity yet, in this manuscript, we are trying to describe it. It may be a manifestation of some allergic response. The allergen(s) could be in the form of ingested food ingredient or additive, or an aeroallergen. Several findings support the idea that DEI may be allergic in nature. First, there is a high prevalence of personal history of atopy (asthma, 21.3%; history of allergies (e.g. eczema and allergic rhinitis) other than asthma, 34%). Both asthma and other allergies occurred in 39 patients (15.6%), and family history of atopy in 93 patients (37%). Second, our study population reveals a high percentage of patients with peripheral eosinophilia (21%). Peripheral eosinophilia was not directly related to tissue eosinophilic infiltrate at any GI site. Finally, we noted, there was a high percentage of patients with positive RAST results (55% of tested patients).

In our study, we noted that biopsies from other GI sites did not show any pathological findings in the majority (>60%) patients. This may suggest that this is a duodenum specific disease. This could be due to the fact that the duodenum is the first absorptive GI surface to get in contact with ingested allergen.

There are no vigorous standards for the normal number of eosinophils in GI mucosal biopsies in asymptomatic children. The best attempt to deal with this limitation was made by Lowichik et al. in Dallas, Texas [5]. They studied intestinal tract mucosa from a series of 44 autopsies of infants and children (duodenum in 38 of them). These patients were between the ages of 3 weeks to 17 years (mean age: 2.2 years) and had died suddenly and unexpectedly, presumably without known gastrointestinal disease. They found that 52% of them had eosinophilic infiltrate from at least one GI site. Although this percentage is less than our finding of 68% in patients with various gastrointestinal complaints, it is still high. This is consistent with our observation and with previous data suggesting a geographic variation with higher eosinophilic counts in the southern United States [5].

We acknowledge that in Lowichik et al study, the patients were presumed to be without known gastrointestinal symptoms, yet we know that GI gastrointestinal complaints are fairly common in childhood and it is possible that some of them might have had GI complaints. Moreover, we do not know the effect of death on eosinophilic mucosal infiltration. In addition, we do not know the reasons for their deaths, which might have relevance to intestinal inflammation, such as anaphylaxis. Nevertheless, for the purpose of comparison we will assume that their findings represent a background eosinophilic count in asymptomatic children.

In an effort to determine whether eosinophilic infiltrate at certain GI sites are more relevant than at other sites, we compared different GI sites. In Lowichik series, the duodenum was the least likely GI site to be involved with eosinophilic infiltrate (18%) compared to the terminal ileum and colon (42% and 28%, respectively). Since those children were presumed to be previously healthy, the relatively high prevalence of eosinophilic infiltrate in the colon and terminal ileum may represent a high background count with no clinical significance. Therefore, the lower prevalence of duodenal eosinophilic infiltrate (18%) in comparison with our findings in symptomatic patients (37%) suggests that this may reflect a important pathology.

Our findings are higher than previous reports [5,6,7]. Lowichik and her group reported an endoscopic biopsy series conducted in 1993-1994, for eighty-four children with abdominal pain. Eosinophilic infiltrates were found in 33% of the children at some GI site, and only 12% had duodenal eosinophilic infiltrate. Again eosinophilic infiltrate was more common in the terminal ileum and different parts of the colon (24% and 42-50%) [5,6]. Whittington et al, in a series of 77 duodenal biopsies in 1983-1984, from children with various GI complaints mainly abdominal pain and vomiting, reported no patients with significant eosinophilic infiltrate [7]. A possible explanation for this difference could be related to the time difference between our study and previous studies, which coincides with a dramatic increase in the incidence of allergic disorders over the last decade, or may be related to our larger sample size. There is no agreement on an acceptable upper limit of normal number of eosinophils in the duodenal mucosa "normal background" [5,7,8,9]. About half of our patients has 10-20 eos /hpf, and another half had > 20 eos /hpf. Factors; other than the number of eosinophils; might play a role [10,11,12], but this was not evaluated in this study.

There is a lack of consensus on the management of patients with GI eosinophilic infiltrate [6, 13,14,15]. This was evident by the various modalities used to treat these children. Most of the modalities used were symptomatic in nature. It was not possible to identify which medication was more effective, because a large percentage of the patients used more than one medication (either simultaneously or sequentially). Additionally the effect of diet modification is unclear. Since a large percentage of patients (40.0%) were still on medications to control their gastrointestinal complaints at the time of follow-up, one can conclude that their response to different treatments was not satisfactory. It is evident that the treating physicians recommended diet modification, of some sort, frequently (24.5%). One in ten patients was judged sick enough and their complaints allergic in origin to be started on elemental diet. After 12-36 months, a significant percentage of patients were still symptomatic (failure to thrive: 57%, nausea: 55%, and abdominal pain: 44%) and 40% were still on medications to control their symptoms. This indicates chronicity and the treatment used was not effective. It was important to know that fourteen (5.6%) of children with DEI developed IBD after only 12-36 months. Whether DEI is a predictor of pediatric IBD remains to be proven.

5. CONCLUSION

Histologic eosinophilic infiltrate of the duodenal mucosa appears common. It appears most commonly in children with allergy. There are no specific symptoms associated with DEI and it appears to be chronic. Symptoms remain persistent in a significant number of patients despite therapy. Close observation of patients with DEI is warranted since a small number of patients may develop IBD. A universally accepted scale for quantifying gastrointestinal mucosal eosinophilia is needed. As a consequence of the design of this study; limited new information was added to the current understanding of eosinophilic infiltrate of the digestive tract. Further studies looking at the activity of eosinophils in the GI mucosa are warranted.

CONSENT

Not Applicable

ETHICAL APPROVAL

Not Applicable

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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