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Effect of Tissue Eosinophilia on the Disease Outcome of Pediatric With Inflammatory Bowel Disease (IBD)

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ABSTRACT

Background: It seems that the presence of tissue eosinophils in IBD patients can provide more information to predict the prognosis and outcome of the disease, especially in children. However, there is very limited evidence in this regard. Here, we designed a retrospective study to investigate the effect of tissue eosinophils on children with IBD.

Methods: We analyzed 73 pediatric patients with IBD with a retrospective study design who underwent measurement of fecal calprotectin (FC) and colonoscopy. IBD patients with and without tissue eosinophils diagnosed according to guidelines were compared in terms of disease activity, clinical symptoms, and other clinical outcomes.

Results: In the present study, 37 patients without and 36 patients with tissue eosinophilia were investigated. This study indicated a significant relationship between the mean eosinophil and Mayo score as the severity of the UC disease based on colonoscopy. However, the findings of the present study did not report any difference between the two groups in terms of disease severity markers and disease activity (base on pediatric ulcerative colitis activity index (PUCAI) for UC and the pediatric Crohn's disease activity index (PCDAI) for CD). The findings showed that the mean eosinophilia in cecum/ascending and rectum/sigmoid colon is significantly higher in pediatric IBD with tissue eosinophilia.

Conclusion: Although no significant finding was found between tissue eosinophil and disease outcomes it seems that there is a significant linear relationship between mean tissue eosinophil and Mayo score.

1 | Introduction

Inflammatory bowel diseases (IBD) are chronic, immune-mediated conditions that include two distinct phenotypes: Crohn's disease (CD) and ulcerative colitis (UC) [1, 2]. The incidence of IBD is rapidly increasing in both adults and children, even in countries with historically low prevalence [3]. Notably, 20%–30% of IBD cases are diagnosed in childhood, and childhood-onset IBD has been reported to be associated with increased disease activity and a higher risk of complications [4]. To date, numerous studies have shown that long-term outcomes improve with appropriate initial treatment and regular follow-up, taking disease activity into account [5].

Although the main IBD pathogenesis is still unclear, the role of immune mediators and inflammations in several triggers was investigated as a severity predictor. Recent advances suggest that both innate and adaptive immune responses play crucial roles in the pathogenesis of IBD. While dysregulated innate immunity can trigger inflammation, the adaptive immune response—particularly T-cell activation—further propagates the chronic intestinal inflammation characteristic of the disease [6].

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Furthermore, architectural damage caused by the transmigration of polymorph nuclear (PMN) leukocytes has been demonstrated from biopsies [7]. The leukocyte infiltration is followed by different cytokine and inflammatory products causing intestinal integrity disruption and forming ulcers, crypts, and abscesses [8, 9].

Since the intestinal mucosa is exposed to unique antigens and microbiomes, maintaining intestinal homeostasis requires effective communication and crosstalk between intestinal cells and leukocytes [10]. Unlike other tissues such as the skin or lungs, eosinophils reside in the gastrointestinal lamina propria and play a crucial role in epithelial interactions with the environment, contributing to gastrointestinal health under normal conditions [11]. Eosinophils are granulocytic leukocytes traditionally associated with allergic and atopic diseases, such as asthma and helminthic infections. They are classically linked to T-helper 2 (TH2) cytokines, including interleukin (IL)-4, IL-5, IL-10, and IL-13 [12]. To date, eosinophils have been implicated in the pathogenesis of various diseases, such as asthma, eosinophilic esophagitis, and certain gastrointestinal disorders, highlighting their role beyond allergic responses. However, IBD remains subject to review, and the various studies establish controversial results [11]. In this regard, some studies have shown elevated tissue eosinophils, as well as increased levels in peripheral blood, due to the production of specific eosinophil granule proteins in active or fulminant IBD. Moreover, the relationship between eosinophils and early IBD manifestations has been demonstrated. On the other hand, other investigations have highlighted the role of eosinophils in tissue remodeling and the production of anti-inflammatory mediators [13].

However, eosinophils are not the histologic IBD landmarks; the quality of histopathologic diagnosis depends on extra helpful information, which can provide a more accurate and early diagnosis. Also, it could provide more information to predict the disease prognosis and outcome, especially in children. Here, we designed a retrospective study to investigate the effect of tissue eosinophils on children with IBD.

1.1 | Methods

A retrospective study was conducted on 73 pediatric patients with IBD aged between 6 and 18 years. The study took place at the Children's Medical Center Hospital in Tehran, Iran, between January 2022 and October 2023. This study was approved by the research council and ethics committee of Tehran University of Medical Sciences, Tehran, Iran (IR.TUMS.MEDICINE.REC.1400.951). The patients had colonoscopy and laboratory tests. The diagnosis of IBD was established using endoscopic exams, laboratory tests, and clinical examinations, and confirmed by a pediatric gastroenterology specialist. Since all the patients were freshly diagnosed and all data was gathered at the time of diagnosis, none of them received treatment with corticosteroids, azathioprine, or methotrexate. Exclusion criteria included prior colon surgery, uncertain colitis, infection, cancerous diseases, blood disorders, heart or lung conditions, autoimmune disorders, enlarged liver or spleen, and kidney failure. Age, gender, disease activity, and test results were documented at referral after obtaining informed consent from the patient or guardian. To account for the high occurrence of IBD in Iranian pediatrics, the minimum required sample size was determined to be 65 subjects. This calculation was based on a power analysis, assuming a confidence level of 95%, a statistical power of 80%, and an estimated prevalence of IBD in the target population of approximately 10%–15% according to previous epidemiological studies. A margin of error of 5% was considered acceptable to ensure statistical reliability. The final sample size was adjusted to account for potential dropouts and incomplete data.

1.1.1 | Definitions of Tissue Eosinophilia

According to our knowledge, so far there is no study or guideline for the pathological count of accepted tissue eosinophil count in children with IBD. Therefore, we used tissue eosinophil counts obtained from IBD adult patients with eosinophilic gastrointestinal disorders (EGID). EGID is described as recurrent or persistent gastrointestinal symptoms with a pathological increase in eosinophil count per high-power field at the affected gastrointestinal location. The pathological counts of eosinophil counts are accepted as greater than 20 per high-power field (hpf) for the mucosa of the duodenum, jejunum, and ileum [14]; greater than 50/hpf for the right colonic mucosa; greater than 35/hpf for the transverse colonic mucosa; and greater than 25/hpf for the left colonic mucosa, as per Turner et al. [15].

1.1.2 | Specimen Histological Assessments

A board certified pediatric pathologist evaluated all colonic tissue sections stained with hematoxylin and eosin from participants with “colonic eosinophilia.” The entire specimens were examined, and the region with the highest concentration of eosinophils was chosen to count the maximum number of eosinophils per high-powered field (eos/HPF) at a magnification of ×40 with a field size of 0.26 mm^2.

1.1.3 | Biochemical Studies

The patient collected fecal samples for calprotectin measurement at home the day before and delivered them refrigerated to the laboratory for examination. Following the freezing and thawing process, all fecal samples were analyzed using an enzyme-linked immunosorbent assay method (Ridascreen Calprotectin test; R-Biopharm, Darmstadt, Germany). Serum levels of Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) were measured using a colorimetric enzyme-linked immunosorbent assay (R&D Systems, Minneapolis, MN) as per the manufacturer's instructions.

1.1.4 | Assessment of Disease Activities

Patients were assessed using the pediatric ulcerative colitis activity index (PUCAI) for UC and the pediatric Crohn's disease activity index (PCDAI) for CD to determine their clinical

status in terms of diagnosis, remission, or active disease. The patients' PUCAI and PCDAI scores were considered when they were ≥ 10 points for active disease and < 10 points for the remission phase.

1.1.5 | Assessment of Simple Endoscopic Score for Crohn's Disease (SES-CD) and Mayo Score

The SES-CD is scored based on four endoscopic variables (area of affected surface, presence and size of ulcers, extent of ulcerated surface, and presence of stenoses) in the five intestinal segments mentioned above. The total SES-CD score range is 0–60, with each section ranging from 0 to 12 points. The Mayo score is a frequently utilized disease activity index in UC. It consists of four components: rectal bleeding, stool frequency, physician assessment, and endoscopic appearance. The rating scale ranges from 0 to 3 for each part, resulting in a total score between 0 and 12.

1.1.6 | Statistical Analysis

The distribution of the variables was confirmed to be normal using the Kolmogorov–Smirnov test. One-way analysis of variance (ANOVA) was then employed to compare quantitative variables among the three groups, while a *T*-Test was used for comparisons between the two groups. Chi-square or Fisher exact statistical test was utilized for qualitative variables. Spearman's rank correlation was used to analyze the relationship between mean tissue eosinophil levels and Mayo and SES-CD scores. SPSS 25.0 statistical software was used for all analyses, with statistical significance set at a *p*-value below 0.05.

2 | Results

In the present study, 73 children with IBD (37 patients without tissue eosinophilia and 36 patients with tissue eosinophilia) were investigated. The mean age of patients in the two groups is shown in Table 1. The mean age was higher in pediatric patients without tissue eosinophilia. Additionally, in this study, 40.5% of patients without tissue eosinophilia and 50% of those with tissue eosinophilia were boys. Other demographic information, biomarkers, and characteristics of the two groups are presented in Table 1.

The findings of the study indicated that the mean calprotectin levels, as well as the mean and maximum tissue eosinophil counts, were significantly higher in pediatric patients with tissue eosinophilia compared to those without tissue eosinophilia ($p < 0.05$). A significant difference was also observed regarding the type of IBD between the two groups, with a significantly higher number of individuals with UC in the tissue eosinophilia group compared to those with CD. Moreover, the mean Mayo score and SES-CD did not show a significant difference between the two groups, indicating no difference in IBD severity (for UC and CD patients, respectively) based on colonoscopy findings. Disease activity, as assessed by the mean PUCAI and PCDAI, did not show a significant difference between the two groups. However, levels of inflammatory markers, including ESR and CRP, were significantly higher in IBD patients with tissue eosinophilia compared to those without tissue eosinophilia.

TABLE 1 | Demographic information, biomarkers, and other characteristics between IBD patients with or without tissue eosinophilia.

	Diagnosis		
Variables	**Without tissue eosinophilia (*n* = 37)**	**With tissue eosinophilia (*n* = 36)**	***p*[a]**
Boy, *N* (%)	18 (50.0)	15 (40.5)	0.417
Age (months)	98.80 (61.87)	82.75 (56.71)	0.235
FC (μg/g)	628.42 (451.87)	895.00 (187.21)	**0.018**
Mean tissue eosinophil	15.64 (8.73)	32.47 (15.91)	**< 0.001**
Tissue eosinophil maximum	23.40 (16.08)	40.84 (21.37)	**< 0.001**
Type of IBD			
UC	13 (44.8)	27 (61.3)	**0.039**
CD	16 (55.1)	17 (38.6)	
Mayo score	6.00 (1.41)	8.00 (1.60)	0.517
SES-CD	15.00 (4.22)	19.00 (5.08)	0.662
CRP (mg/l)	1.15 (1.35)	3.98 (3.07)	**< 0.001**
ESR (mm/h)	10.90 (8.15)	20.60 (12.17)	**< 0.001**
WBC	6719.16 (2271.09)	7451.41 (5142.81)	0.218
Disease activity based on			
PUCAI	28.78 (9.8)	35.20 (10.03)	0.204
PCDAI	17.56 (7.6)	19.29 (6.9)	0.543

Note: Bold value means statistical significant of $p < 0.05$.
Abbreviations: CD, Crohn's disease; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; FC, fecal calprotectin; PCDAI, pediatric crohn's disease activity index; PUCAI, pediatric ulcerative colitis activity index; SES-CD, simple endoscopic score for Crohn's disease; UC, ulcerative colitis; WBC, white blood count.
[a]Obtained from ANOVA for continuous variables and Chi-square of independence for Categorical variables. Values are mean ± SD (95% CI) or *n* (%).

Information on clinical examinations between IBD patients with and without tissue eosinophilia is also presented in Table 2. The findings revealed a significant difference in the presence of bleeding between the two groups, with a higher number of IBD patients experiencing bleeding in the group without tissue eosinophilia. However, no significant differences were observed regarding constipation, diarrhea, nocturnal symptoms, or oral ulcers between the two groups.

Table 3 illustrates the distribution of duodenal and colonic eosinophilia in IBD patients with and without tissue

TABLE 2 | Clinical examination data between IBD patients with or without tissue eosinophilia.

Variables	Diagnosis		
	Without tissue eosinophilia ($n=37$)	With tissue eosinophilia ($n=36$)	p^a
Constipation, *N* (%)	1 (2.8)	3 (8.1)	0.317
Diarrhea, *N* (%)	25 (69.4)	20 (54.1)	0.176
Bleeding, *N* (%)	30 (83.3)	20 (54.1)	**0.007**
Nocturnal symptoms, *N* (%)	8 (22.2)	3 (8.1)	0.092
Oral ulcers, *N* (%)	6 (16.7)	2 (5.4)	0.124

Note: Bold value means statistical significant of $p < 0.05$.
[a]Obtained from Chi-square of independence for Categorical variables. Values are *n* (%).

TABLE 3 | Evaluation of duodenum and colonic eosinophilia distribution between IBD patients with or without tissue eosinophilia.

Variables	Diagnosis		
	Without tissue eosinophilia ($n=37$)	With tissue eosinophilia ($n=36$)	p^a
Duodenum	18 (9.91)	23 (10.59)	0.874
Terminal ileum	22 (11.34)	38 (13.97)	0.541
Cecum and ascending	24 (12.18)	54 (18.51)	**0.015**
Transverse and descending	31 (14.01)	42 (16.20)	0.214
Rectum and sigmoid	29 (13.66)	57 (19.88)	**0.025**

Note: Bold value means statistical significant of $p < 0.05$.
[a]Obtained from Chi-square of independence for Categorical variables. Values are *n* (%).

eosinophilia. The findings indicated that the mean eosinophil count in the cecum/ascending colon and rectum/sigmoid colon was significantly higher in pediatric IBD patients with tissue eosinophilia compared to those without. However, no significant differences were observed in other colonic and duodenal regions.

Table 4 presents the correlation between mean eosinophil counts and the Mayo score and SES-CD score. The findings showed a significant correlation between the mean eosinophil count and the Mayo score, reflecting UC severity based on colonoscopy. However, no significant correlation was found between the mean eosinophil count and the SES-CD score.

TABLE 4 | Correlation between mean tissue eosinophil and Mayo and SES-CD scores.

Mean tissue eosinophil	*B* coefficient	R^2	p^*
Mayo score	−2.278	0.056	**0.043**
SES-CD	−0.081	0.003	**0.672**

Note: Linear regression analysis has been used. Bold value means statistical significant of $p < 0.05$.
*p-value is less than 0.05 and significant.

3 | Discussion

In our study, the findings indicated an earlier diagnosis of IBD in the group with tissue eosinophilia. We assumed that tissue eosinophilia might be a prominent primary symptom, leading to an earlier diagnosis. Early recognition of IBD in children requires the timely referral of suspected patients, prompt medical attention to symptoms, and diagnostic endoscopy [16]. A retrospective study involving 22 pediatric patients diagnosed with IBD suggested a significant correlation between rectosigmoid eosinophilia and other findings, including crypt formation in the colon and inflammatory markers, with early diagnosis [17]. Another study on 56 children with functional abdominal pain disorders (FAPDs), 52 children with Crohn's disease, and 23 children with ulcerative colitis observed significantly higher eosinophil counts in the stomach and colon in both IBD and FAPD patients, regardless of endoscopic detection [18].

Another finding in our study was a significantly elevated inflammatory biomarker with tissue eosinophilia in IBD patients compared to the group without tissue eosinophilia. In patients with milder symptoms such as chronic abdominal pain, diarrhea, and growth failure, significant changes in the levels of serum inflammatory biomarkers such as CRP, ESR, and fecal inflammatory biomarkers (calprotectin) can increase the likelihood and severity of IBD [19]. The observed correlation between tissue eosinophils and inflammatory markers such as CRP, ESR, and calprotectin, but not with PUCAI and PCDAI, may be due to differences in what these measures reflect. CRP, ESR, and calprotectin are objective biomarkers of systemic and intestinal inflammation, whereas PUCAI and PCDAI are clinical indices that incorporate subjective symptoms and physician assessments, which may not directly correlate with tissue-level eosinophilic infiltration. Additionally, variations in disease presentation and treatment effects may contribute to this discrepancy.

A study on 253 children examining the relationship between eosinophils and fecal calprotectin (FC) demonstrated that an increase in FC levels could indicate the likelihood of an organic gastrointestinal (GI) disease such as IBD and help distinguish it from other eosinophilic gastrointestinal disorders [20]. Furthermore, a retrospective analysis of 36% of children diagnosed with IBD reported "colonic eosinophilia," significantly

elevated ESR, hematochezia, and chronic changes in their biopsy results [21].

We also found that patients with tissue eosinophilia had a significantly lower rate of GI bleeding. Although most patients in the tissue eosinophilia group had UC—and several studies have shown that patients with ulcerative colitis experience GI bleeding more frequently than those with Crohn's disease [22], we hypothesized that eosinophils play a protective role in gastrointestinal epithelia and reduce bleeding by promoting a pro-coagulant state in UC patients. An experimental study conducted in 2017 by Stephen Uderhard demonstrated that eosinophils contribute significantly to thrombin formation and thrombus stabilization, as well as physiological hemostasis [23]. Furthermore, an investigation in UC-diagnosed patients revealed that active eosinophil levels were higher during the inactive phase compared to active UC phases, suggesting their role in tissue remodeling, fibroblast and myofibroblast transformation, and procollagen production through eosinophil-derived TGF-β1, IL-13, and IL-5 release [24].

Although eosinophils have been linked to tissue damage and the active phase of IBD, limited research has been conducted on the localization of eosinophil-related abnormalities in colonoscopy. We hypothesize that our findings on eosinophilia in different parts of the colon may be influenced by various factors affecting eosinophil distribution, as well as the role of eosinophils in modulating tissue remodeling and inflammation at different stages of different types of IBD. A comparison between children with CD and those with UC showed that children with UC had significantly higher eosinophil counts in the ascending colon, descending colon, sigmoid colon, and rectum than those with CD. These findings are consistent with our study. However, in the previous study, after excluding tissue specimens with macroscopically active inflammatory lesions, no significant differences in tissue eosinophil counts were observed, except in the ascending colon [18]. Moreover, a histopathologic retrospective study on children diagnosed with colonic eosinophilia identified IBD as the main phenotype in groups with elevated inflammatory markers and demonstrated significant colonic eosinophilia in the rectosigmoid colon compared to the control group [21]. Additionally, a study using H&E (Hematoxylin and Eosin) staining on 276 colonic slides showed a higher mean eosinophil count per mm^2 in the right colon of UC patients compared to other groups, while in the left colon, the mean eosinophil count was higher in patients with a history of CD [25]. The study does not provide an in-depth discussion on the differences in eosinophil involvement between UC and CD. While eosinophils play a role in both conditions, their distribution and function differ. In UC, eosinophilic infiltration is typically more pronounced in the lamina propria and is associated with mucosal inflammation and barrier dysfunction. In contrast, CD is characterized by a more heterogeneous eosinophil presence, often linked to transmural inflammation and granuloma formation. The differential role of eosinophils in these diseases may be influenced by variations in cytokine signaling, immune cell interactions, and microbiota composition, warranting further investigation.

A further important finding of our study was the significant relationship between mean eosinophil count and the Mayo score as an indicator of UC and UC activity, while no significant correlation was observed between mean eosinophil count and the SES-CD score as a specific marker of CD activity. Although in our study, the Mayo score and SES-CD did not show a significant difference between patients with tissue eosinophilia and those without eosinophilia, higher Mayo scores could still be associated with increased tissue eosinophilia, indicating a potential role of eosinophils in UC pathogenesis. Consistent with our study, a cohort study on pediatric patients diagnosed with UC revealed significant tissue and peripheral eosinophilia, which was associated with increased tissue inflammation as well as greater clinical severity at diagnosis [26]. On the other hand, a retrospective study of 77 children diagnosed with CD found an association between eosinophils and IL-33 with fibrosis and strictures observed on endoscopy [6].

Eosinophils can damage the gastrointestinal mucosa in different ways. In addition to cytokine release and inflammatory mediators causing mucosal damage, one study showed that colonic motility disorders and alterations in the enteric nervous system were due to eosinophil infiltration and disease severity in the gastrointestinal tract [27]. A study of 225 children with very early-onset inflammatory bowel disease (VEO-IBD) found a higher incidence of crypts with increased eosinophil infiltration in the lamina propria on endoscopy [28]. The role of eosinophils in IBD pathogenesis has been implicated through eosinophil cationic protein (ECP), eosinophil peroxidase (EPO), and the demonstrated production of eosinophil-derived protein X (EPX) in active colitis [29]. Additionally, it has been shown that the IBD relapse rate is significantly higher with increasing eosinophil and neutrophil counts in the lamina propria of the gastrointestinal tract [30].

While several studies have indicated the role of eosinophils in the inflammatory response in IBD patients, some researchers have highlighted the anti-inflammatory role of eosinophils, demonstrating their ability to enhance fibroblast activity and produce protectin D1 (PD1), a self-regulating mediator that suppresses chemotaxis [31, 32]. Furthermore, a cohort study found an increased risk of disease flares in biopsy samples where neutrophils were more prominent than eosinophils [13]. Another large study of 368 pediatric patients showed a high number of eosinophils in the colon in the treatment group, which was associated with less severe inflammation on endoscopy [33]. This controversy may stem from the potential misestimation of eosinophil counts due to the influence of certain medications. Specifically, drugs such as prednisolone and mesalazine have been shown to affect eosinophil levels, potentially leading to eosinophilia [34, 35]. Although none of the patients were treated with these drugs at the beginning of our study, it could be due to the use of these drugs in the years before the diagnosis of the disease.

In addition, the function of eosinophils differs between UC and CD. CD is characterized by several features of TH1 inflammation, whereas UC is more closely associated with allergic responses [36]. It has been shown that TH2 plays a similar role in both UC and atopy [37, 38]. A study of 50 patients diagnosed with UC found a significant association between UC and several allergy markers, but without significant eosinophilia in colon tissue. Histological examinations and colonoscopy were used to determine disease severity [36]. On the other hand, it has been shown that in UC

patients, IL-5 and IL-13 secretion is increased compared to CD patients, leading to a higher presence of eosinophils in the intestinal lamina propria [39]. Moreover, similar to the asthmatic lung, several studies have demonstrated that the expression of intercellular adhesion molecule 1 (ICAM-1) and vascular cell adhesion molecule 1 (VCAM-1) plays a role in the intestinal mucosa of IBD patients [40]. Consistent with these findings, a study of 14 UC colon samples revealed upregulation of ICAM-1 and VCAM-1 in UC patients [41]. Furthermore, a study by Elizabeth Forbes showed that the β2-integrin/ICAM-1-dependent pathway plays a crucial role in the recruitment of eosinophils to the gastrointestinal tract [42]. Another factor contributing to the varying results regarding eosinophils and IBD may be differences in follow-up duration. One study specifically conducted on UC patients assessed only tissue and peripheral eosinophils in relation to prognosis and short-term outcomes, without long-term follow-up [26].

Our retrospectively designed study had limitations ranging from a small study population to some missing data for some individuals as well as uncertainty about cause and effect relationships due to the study design.

4 | Conclusion

In conclusion, our study highlights the pivotal role of tissue eosinophilia in early IBD diagnosis in children, emphasizing its correlation with inflammatory biomarkers. Understanding this relationship could offer new insights into predicting IBD behavior, particularly in pediatric cases, based on endoscopic findings and tissue eosinophil levels.

Acknowledgments

The authors have nothing to report.

Ethics Statement

This study was approved by the research council and ethics committee Tehran University of Medical Sciences, Tehran, Iran (IR.TUMS.MEDICINE.REC.1400.951). We confirm that all methods were carried out in accordance with relevant guidelines and regulations. Also, we confirm that informed consent was obtained from a parent and/or legal guardians of the participants (control as well as patients).

Consent

The authors have nothing to report.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

Data is available upon request from the corresponding author for the article due to privacy/ethical restrictions.

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