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Detection of Eosinophilic Cell-free Granules Based on Expression of CCR3 and MBP Markers in Colonic Biopsy of Pediatric Patients with Suspected and Confirmed Eosinophilic Colitis

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ABSTRACT

Background: Eosinophilic colitis (EC) is a rare eosinophilic gastrointestinal disorder with increasing frequency in recent years. Although normal eosinophil density varies substantially by colonic segment, several proposed eosinophil thresholds have been used in the literature to support the diagnosis in the appropriate clinical context. However, some patients with clinical features suggestive of eosinophilic colitis (EC) do not demonstrate increased tissue eosinophil counts on histopathologic examination.

Objective: To compare eosinophil-derived cell-free granules based on expression of their surface markers between two groups of patients with symptoms consistent with EC: those with increased tissue eosinophils and those without tissue eosinophilia.

Methods: This study included 10 pediatric patients with histologically confirmed EC and 13 patients with clinical suspicion of EC. Eosinophil-derived cell-free granules were evaluated in colonic tissue samples using immunohistochemistry (IHC), with antibodies against MBP and CCR3.

Results: Eosinophil-derived cell-free granules were detected in all specimens from patients with suspected EC and in the majority of specimens from patients with confirmed EC. Degranulating eosinophils were identified in all specimens from both groups, although the proportion of degranulating eosinophils varied among patients. Furthermore, the abundance of granules was significantly associated with the percentage of degranulating eosinophils.

Conclusion: Our findings indicate that IHC can be used to detect eosinophil-derived granules in colonic tissue. The presence of cell-free eosinophil granules with varying abundance, along with evidence of eosinophil degranulation in all specimens from patients with suspected EC, may provide supportive histopathological features that contribute to improving the diagnostic assessment of EC.

Keywords: Colitis, Eosinophilic enteropathy, Eosinophil granule, Food hypersensitivity, Immunohistochemistry

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INTRODUCTION

Eosinophilic gastrointestinal diseases (EGIDs) are a group of uncommon chronic inflammatory disorders characterized by eosinophil-predominant inflammation of the gastrointestinal tract and a broad spectrum of gastrointestinal symptoms affecting both children and adults (1). Among the EGIDs, eosinophilic colitis (EC) is the least prevalent subtype. Currently, no universally accepted histopathological criteria exist regarding the eosinophil count, tissue morphology, or clinical features required for its diagnosis. Unlike the esophagus, where eosinophils are normally absent, eosinophils are physiologically present in the colonic mucosa. Therefore, the diagnosis of EC is generally based on an increased eosinophil density in the appropriate clinical context after excluding other causes of colonic eosinophilia, including parasitic diseases, drug-induced reactions, inflammatory bowel disease (IBD), and celiac disease. Recent studies have shown that EC possesses a distinct molecular profile compared with other gastrointestinal inflammatory disorders, such as IBD, highlighting the need for further investigation (2). Common symptoms of EC include abdominal pain, diarrhea, hematochezia or dysentery and anemia, and weight loss (3,4). Although EC is the least common subtypes of EGID , its reported incidence and prevalence have increased in recent years (5,6). Expanding the clinical and pathological knowledge of EC, together with determining its true prevalence in the population, will improve our understanding of the disease and contribute to the development of more accurate diagnostic strategies and effective therapeutic approaches (7,8). Eosinophils contain cytoplasmic specific granules, including MBP, eosinophil cationic protein (ECP), eosinophil peroxidase (EPX), and eosinophil-derived neurotoxins (EDN), which can be released into the extracellular space through degranulation. Although disease-specific patterns of eosinophil degranulation have not been fully characterized, accumulating evidences suggests that eosinophil degranulation plays an important role in tissue inflammation and the pathogenesis of gastrointestinal diseases (9). In addition to granule proteins, eosinophil granules express membrane-associated receptors, including interferon γ receptor (IFNγ-R) and CCR3, which remain detectable on extracellular granules following degranulation (10).

Given the increasing recognition of EC and the likelihood that some patients with characteristic clinical features are underdiagnosed because they do not meet conventional tissue eosinophil thresholds, we sought a diagnostic approach for patients suspected of having EC who present with all typical clinical features of the disease but lack sufficient tissue eosinophilia. Given that some eosinophils may rupture and release their granules upon inflammation, and that the presence of cell-free granules can serve as a proxy for a higher eosinophil burden, we investigated cell-free granules in biopsy specimens from two patient groups, those with confirmed EC and those with suspected EC

MATERIAL AND METHODS

Study Population This case-control study included 13 pediatric patients with suspected EC and 10 patients with confirmed EC. There was no statistically significant difference between the two groups regarding age and sex.

Biopsy specimens were obtained from the clinicopathologic database of Roshan Azma pathobiology laboratory (a referral center for pediatric gastrointestinal pathology) in Tehran, Iran, spanning the years 2017 to 2021. All samples were derived from confirmed and suspected EC patients whose specimens had been submitted to this laboratory.

Although no validated criteria exist for normal colonic eosinophil count, nor specific protocols for confirming EC, and studies are still underway to establish normative values and the factors that influence them (11), patient

selection was based on consensus confirmation by both a pediatric gastroenterologist and an experienced pathologist. According to the literature, the accepted eosinophilic thresholds for diagnosing eosinophilic colitis are >100 eosinophils per high-power field (Eos / HPF) for the right colon, >84 Eos / HPF for the transverse and left colon and >64 Eos / HPF for the rectosigmoid (12,13). Accordingly, patients in the confirmed EC group were diagnosed based on physician assessment of relevant symptoms, exclusion of other similar conditions (e.g., celiac disease, ulcerative colitis, and Crohn's disease) and colonic eosinophilia meeting or exceeding the respective threshold. Patients in the suspected EC group were similarly selected based on physician assessment of relevant symptoms and exclusion of other similar diseases, but with colonic eosinophilia <64 Eo / HPF. Thus, the suspected EC group presented with all the clinical features of the confirmed group, differing only in that their tissue eosinophil count did not reach the diagnostic threshold.

Patient demographic and clinical data, including age, sex and history of allergies, were also extracted from the patients' medical records.

Immunostaining

Immunohistochemistry (IHC) was performed on 5-µm sections of formalin-fixed, paraffin-embedded tissue blocks. The staining procedure comprised the following steps: the slides were deparaffinized with xylene, enzyme-treated for antigen retrieval using pepsin solution (Abcam, USA), blocked with blocking buffers (H_2O_2 and bovine serum albumin or BSA with sheep serum) and then incubated with primary antibodies against MBP (mouse, clone BMK-13, 1:25, Bio-rad USA) and CCR3 (rabbit polyclonal, 1:50, MyBioSource, USA). Slides were then incubated with a horseradish peroxidase (HRP)-labelled anti-mouse polymer secondary antibody and alkaline phosphatase (AP)-labelled anti-rabbit polymer secondary antibody (Abcam double stain IHC kit: M&R on human tissue, USA). Finally, they were stained with permanent red chromogen (for CCR3) and emerald chromogen (for MBP) (Abcam double stain IHC kit), and counterstained with hematoxylin. Since the esophagus is normally free of eosinophils, healthy esophageal tissue was used for negative control to check for non-specific binding, and healthy colon samples were used to control for the absence of cell-free eosinophil granules under homeostatic conditions. Hematoxylin and eosin (H&E) staining was also performed on all sections.

Analysis

A scoring model was designed by comparing all patient samples and negative controls semi-quantitatively. This semi-quantitative comparative classification was based on the amount of cell-free granules and the intensity of degranulation in different microscopic fields. The mean cell-free granules were categorized on a scale of 0 to +4 (0=none, 1=very low, 2=low, 3=moderate, 4=high). The cell-free granule rate in confirmed and suspected EC samples was determined by visual analysis of 10 microscopic fields per colon biopsy sample at 1000× magnification performed independently by two researchers . IHC results were compared with H&E staining.

Demographic, clinical and pathologic data were entered in SPSS software. The Kolmogorov-Smirnov test was used to evaluate the normality of data distribution. For statistical analysis, age was compared between the two groups using the t-test; sex distribution and allergy history were compared using the chi-Square test; and the comparison of degranulating eosinophils with cell-free granules was performed using the Mann-Whitney U test.

RESULTS

Twenty-three tissue samples from 10 patients with confirmed EC and 13 patients with suspected EC were included.

Table 1: Demographic data and allergy histories in suspected and confirmed EC group.

variables	Suspected EC	Confirmed EC	P-Value
Gender Female/Male Ratio (%)	61.5/38.5	50/50	0.68
Age (Mean ± SD)	5.1±0.7	6.13±1.7	0.13
Food Allergy History (%)	15.4	40	0.34
Other Allergy History (%)	30.8	20	0.66

The mean age ±SD was 6.1±1.7 years in the confirmed EC group and 5.1±0.7 years in the suspected EC group. No significant difference was observed between the two groups ($p>0.05$). The female/male ratio was 50:50 in the confirmed EC group and 61.5:38.5 in the suspected EC group, with no significant difference ($p>0.05$).

Food allergies were reported in 40% of patients with confirmed EC and 15.4% of patients with suspected EC. Other types of allergies (respiratory, skin, etc.) were reported in 20% of patients with confirmed EC and 30.8% of patients with suspected EC. There was no significant difference between the two groups for either allergy category ($P> 0.05$, Table 1).

Immunohistochemistry and H&E findings

Comparing the H&E-stained and IHC-stained slides, it was observed that H&E cannot clearly identify cell-free granules.

Among the 13 specimens from patients with suspected EC, all of them had cell-free granules in varying quantities: 3 specimens (23%) had +1 cell-free granules, 3 (23%) had +2, 4 (31%) had +3 and 3 (23%) had +4.

Among the 10 specimens from patients with confirmed EC, cell-free granules were not observed in 1 specimen (10%), +1 was observed in 2 specimens (20%), +2 in 1 specimen (10%), +3in 5 specimens (50%), and +4 in 1 specimen (10%)(Figure 1a and 1b).

In all specimens of the suspected group and 90% of the confirmed EC specimens, different degrees of cell-free granules were observed. The mean cell-free granule score (on a scale of 0 to 4) was 2.54 in the suspected group and 2.3 in the confirmed group, which was not statistically different (P=0.64, Figure 2).

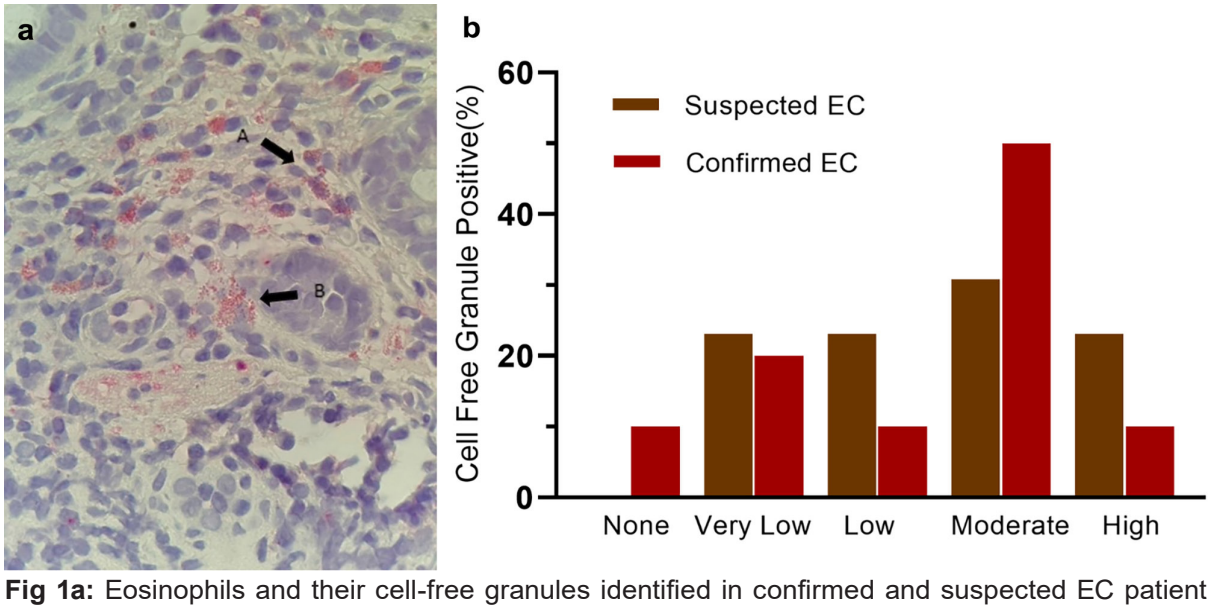

Fig 1a: Eosinophils and their cell-free granules identified in confirmed and suspected EC patient specimens using IHC staining with MBP and CCR3 antibodies (X1000). A: Unruptured eosinophils with granules inside. B: Cell-free granules released from ruptured eosinophils and spread on tissue.
Fig 1b: Comparison of the percentage of specimens with different cell-free granule grades (none to high) between suspected and confirmed EC groups using IHC staining.

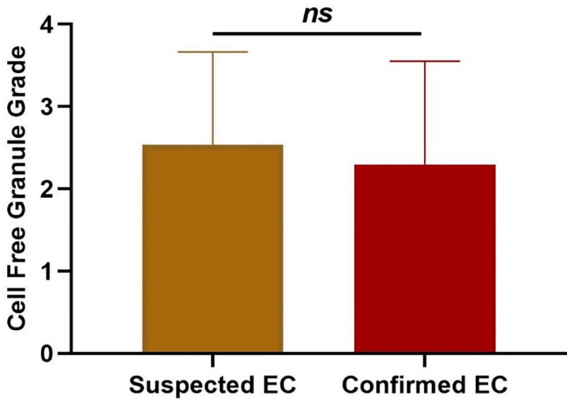

Fig 2: Comparison of cell-free granule detection rates across semi-quantitative grades (0 = none, 1 = very low, 2 = low, 3 = moderate, 4 = high) between confirmed and suspected EC groups using IHC staining (P=0.64).

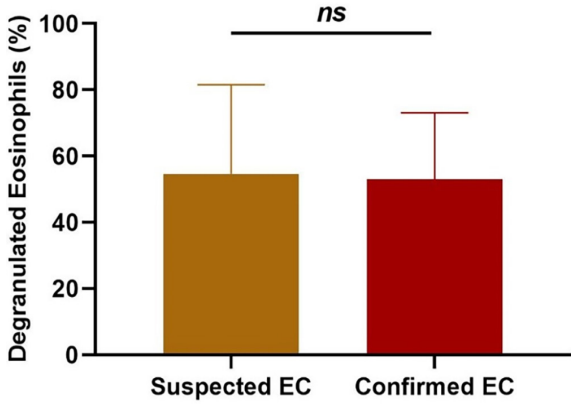

Fig 3: Comparison of the percentage of degranulating eosinophils in IHC-stained specimens in the suspected and confirmed EC groups, analyzed by independent samples t-test (P=0.87).

In the evaluation of IHC slides, some eosinophils were in a degranulating state and had evidence of cytolysis. All 23 suspected and confirmed specimens had degranulating cells ranging from 10% to 90%. These cells were detected in more than 50% of eosinophils in 53.8% of suspected specimens and in 30% of confirmed specimens. The mean percentage of degranulating eosinophils was 54.62% in the suspected group and 53% in the confirmed group. No significant difference was observed between the two groups in terms of degranulating eosinophils (P=0.87, Figure 3).

DISCUSSION

Based on examination of 23 IHC-stained slides, including 10 confirmed and 13 suspected EC patients, we observed that 90% of confirmed and 100% of suspected patients had CCR3+ MBP+ cell-free granules in their specimens. MBP and CCR3 are established markers for detecting eosinophil-free granules in gastrointestinal tissues. MBP is a potent cytotoxic granule protein released during eosinophil degranulation and contributes to mucosal injury in eosinophilic inflammatory disorders of the GI tract, including EC. CCR3, which is present on the surface and granules of eosinophils, mediates the recruitment and activation of eosinophils within the gut mucosa. MBP and CCR3 immunostaining studies in inflammatory bowel diseases and in experimental models have demonstrated their effectiveness in revealing eosinophil cell-free granules in gastrointestinal biopsies, even in cases with low numbers of intact eosinophils (14,15).

The study by Mueller et al., conducted on eosinophilic esophagitis (EoE), reported that detection of degranulation of intraepithelial eosinophils in the distal esophagus in MBP IHC staining is much higher than with H&E staining (16). In our study, comparing IHC with H&E staining, we observed that H&E cannot clearly identify free granules. This suggests that many eosinophils in both suspected and confirmed EC specimens may have undergone cytolysis, releasing their granules into the tissue. Based on this important observation, we propose that detection of cell-free granules could serve as a valuable tool in the evaluation of patients with suspected EC.

Peterson et al. investigated patients with EoE and including those with symptomatic disease but with lower eosinophilia, and found that extracellular MBP was clearly detectable by indirect immunofluorescence even in the low-eosinophilia group (17). Since EoE is the

most common and extensively studied type of EGIDs, and the underlying pathogenic mechanisms are considered similar across EGID subtypes, these observations are consistent with our findings in EC. In our study, varying degrees of degranulation were observed in the majority of samples, which may indicate that the actual eosinophil count was higher than reported, as some eosinophils have been destroyed during the disease process. Additionally, our previous study on esophageal specimens from patients with suspected EoE demonstrated that more than half harbored cell-free eosinophil granules, as detected by double-stained IHC for MBP and CCR3 (14). This earlier finding is in accordance with the present results in suspected EC patients.

The interesting point about colonic tissue eosinophils is that they are present in healthy individuals, and the presence of eosinophils that are about to rupture and release granules—and therefore the observation of free granules—indicates inflammation and disease. Under physiological conditions, piecemeal degranulation, which occurs in response to certain cytokines, is the predominant mechanism of granule release. In this process, the eosinophil remains intact, and only the granular contents of the granules are secreted; thus, free granules are not observed. In contrast, under pathological conditions, granules are typically released via cytolysis, leading to cell destruction and the formation of visible free granules (18). In our study, all 10 confirmed and 13 suspected specimens contained eosinophils showing features of impending rupture and granule release, ranging from 10 to 90% of the eosinophil population. This finding, in addition to the observation of free granules, indicates that even when tissue eosinophil counts are within the normal range, these cells may be in an activated, pro-inflammatory state. Collectively, our results highlight the potential value of assessing eosinophil activation and granule-mediated pathology as complementary diagnostic tools, particularly in eosinophil-rich gastrointestinal disorders characterized by cytolysis.

The absence of a statistically significant difference between the confirmed and suspected groups regarding cell-free granules and degranulating eosinophils supports notion that these two groups share a similar underlying biology. This similarity may further indicate that the currently used diagnostic cutoff (64/HPF) is not adequately precise. As discussed above, these findings reinforce the view that diagnosis based exclusively on eosinophil count is not entirely reliable.

A growing body of evidence indicates that patients with EGIDs and/or their families frequently have a history of allergic diseases. Previous studies have reported that approximately 80% of patients with EGIDs have atopic disorders, with food allergies affecting about 60% of these individuals (19). In the context of eosinophilic colitis (EC), one study found that 41.8% of patients with EC had allergic rhinitis or asthma (20), while another reported food allergies in 18% of patients with EC (21). Moreover, approximately 10% of EGID patients have at least one first-degree relative with an EGID (22). In the present study, a considerable number of patients in both the confirmed and suspected EC groups had a history of allergies. Taken together, these findings support the consideration of allergy history as a useful component in the diagnostic evaluation of EGIDs.

Currently, no consensus exists for the diagnosis of EC. The present study provides preliminary evidence that may help guide the selection of suitable diagnostic tests. Nevertheless, our findings should be interpreted in light of certain limitations. First, the sample size was limited, which reflects both the rarity of the disease and the difficulties encountered in its diagnosis. Second, due to the absence of established clinical criteria for determining disease severity, we were unable to assess whether the degree of eosinophil degranulation correlates with disease severity.

CONCLUSION

The present study demonstrates that IHC is a useful tool for identifying cell-free eosinophil granules in colonic tissue.. The detection of cell-free granules—observed to varying degrees in all suspected EC specimens—and the presence of degranulating eosinophils in both suspected and confirmed EC patients represent potentially valuable findings for describing disease activity and aiding in diagnosis. Although the prevalence of EC is increasing, no established diagnostic criteria currently exist. Therefore, further research is required to explore the different aspects of EC diagnosis and to develop standardized diagnostic criteria.

AUTHORS' CONTRIBUTION

Saghi Khatami: methodology, data curation, writing original draft. Saba Ebrahimi: methodology, revising the manuscript. Fatemeh Elham Mahjoub: pathology evaluation and confirmation, revising the manuscript. Azizollah Yousefi: patient selection, revising the manuscript. Amirhossein Hosseini: patient selection, revising the manuscript. Majid Khoshmirsafa: statistical analysis, revising the manuscript. Fatemehsadat Mousavinasab: study design. Mahboubeh Mansouri: study concept and design, revising the manuscript. Mahdi Shabani: study concept and design, revising the manuscript. Mehrnaz Mesdaghi: supervision, project administration, revising the manuscript.

CONFLICT OF INTERESTS

The authors declare that they have no conflict of interest.

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