ORIGINAL ARTICLE

Low Expression of ICAM-1 in Blood Eosinophils in Patients With Active Eosinophilic Esophagitis

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Abstract

Background: Eosinophilic esophagitis (EoE) is a chronic and isolated inflammation of the esophagus characterized by a marked infiltration of eosinophilic leukocytes. Diagnosis and course of the disease are based exclusively on histopathology. Therefore, patients must undergo several esophageal biopsies, implying a risk associated with the procedure and considerable use of resources.
Objective: The presence of active circulating eosinophils, which are quantifiable through the expression of specific cellular activation proteins in their membrane, could be consistent with histopathological findings, which are currently the only valid parameters in studies on EoE.
Methods: The activity of peripheral blood eosinophils from patients with EoE was analyzed by identifying 5 surface molecules (CD69, IL-5Rα, CD44, ICAM-1, CD63), which are seen to be expressed by the active eosinophils in flow cytometry. The results were compared with the infiltrate of eosinophils present in patients' esophageal biopsies.
Results: ICAM-1 levels decreased significantly in patients with active EoE compared with nonactive EoE patients, allergic patients, and healthy controls. In patients with EoE, an inverse correlation was observed between the number of eosinophils in the esophageal biopsy and the percentage of ICAM-1 expression in peripheral blood eosinophils. No differences were observed for the remaining molecules studied.
Conclusion: Expression of ICAM-1 in blood eosinophils could be a useful noninvasive marker for the diagnosis and assessment of patients with EoE.

Key words: Eosinophilic esophagitis. Eosinophils. Flow cytometry. ICAM-1.

Resumen

Antecedentes: La esofagitis eosinofílica (EoE) es una inflamación crónica y aislada del esófago, caracterizada por una infiltración importante de eosinófilos. El diagnóstico y evolución de la enfermedad se realiza únicamente por estudios histopatológicos. Además, los pacientes se someten a un elevado número de biopsias esofágicas con el riesgo que implica el procedimiento y los recursos utilizados.
Objetivo: Comprobar si la presencia de eosinófilos activos circulantes, mediante la cuantificación de la expresión de proteínas específicas presentes en la membrana de eosinófilos activados, concuerda con los hallazgos histopatológicos aceptados como únicos parámetros válidos para estudios de EoE.
Métodos: Se analizó la actividad de los eosinófilos de sangre periférica de pacientes con EoE mediante la identificación de cinco moléculas de superficie (CD69, IL-5Rα, CD44, ICAM-1, CD63) expresadas en los eosinófilos activos por citometría de flujo. Los resultados se compararon con el infiltrado de eosinófilos presentes en biopsias esofágicas de los pacientes.
Resultados: Se observó que el marcador ICAM-1 está significativamente reducido en pacientes con EoE activa en comparación con pacientes con EoE inactiva, pacientes alérgicos y controles sanos. En estos pacientes, se observó una correlación inversa entre el número de eosinófilos presentes en la biopsia esofágica y el porcentaje de la expresión del ICAM-1 en eosinófilos de sangre periférica. El resto de los parámetros estudiados no presentaban diferencias.
Conclusión: La expresión de ICAM-1 en eosinófilos de sangre periférica podría comportarse como un marcador no invasivo útil en el diagnóstico y seguimiento de pacientes con EoE.

Palabras clave: Esofagitis eosinofílica. Eosinófilos. Citometría de flujo. ICAM-1.

Introduction

Eosinophilic esophagitis (EoE) is a chronic and isolated inflammation of the esophagus characterized by marked infiltration of eosinophilic leukocytes. Although the first cases of adults diagnosed with EoE, which manifested as dysphagia, were described as early as 1975, it was not until 1995 that Kelly et al [1] defined EoE as differing from gastroesophageal reflux and manifesting as esophagitis that does not respond to conventional treatments or improve with an elemental diet [1]. EoE is more frequent in children than in adults and more commonly affects males. The form of presentation varies with age, and the most frequent symptoms are abdominal pain, dysphagia, and food impaction [2]. The histological diagnosis is defined as a cellular infiltration of the squamous epithelium with ≥15-20 eosinophils per high-power field.

EoE frequently occurs in atopic patients, suggesting that recruitment of eosinophils in the esophagus may be a response to environmental antigens in genetically predisposed individuals [3]. High levels of IgE have also been found in the tissues of patients with EoE, although the role of IgE in pathogenesis is unclear [4]. Treatment is based on food restriction [5] and may be empirical or targeted (if data from skin tests or IgE determinations are available) and pharmacological (proton pump inhibitors [PPIs] or corticosteroids) [6].

Specific noninvasive blood markers of the disease have not been identified to date [7,8], and although high levels of specific IgE and peripheral eosinophilia are reported, they are not present in all patients and are generally recorded in patients with mild disease [9]. Diagnosis, disease, course and response to treatment are based exclusively on histopathology, namely, the number of eosinophils in the esophageal biopsy specimen (>15), which is taken via endoscopy. Patients undergo several esophageal biopsies. The procedure is risky and involves considerable use of resources.

Easily applied noninvasive methods would be highly desirable. Therefore, we hypothesize that parameters reflecting both the number of eosinophils and their state of activation in peripheral blood would be easy to determine noninvasively as a marker for diagnosis and assessment of response to treatment in EoE. The presence of active circulating eosinophils, which are quantifiable through the expression of specific cellular activation proteins in their membrane, may be consistent with histopathological findings, which are currently the only valid parameters in EoE studies.

Material and Methods

The activity of peripheral blood eosinophils from patients with EoE was analyzed by identifying surface molecules expressed by activated eosinophils using flow cytometry. Samples for peripheral blood were collected in tubes containing EDTA-K, and 100 µL was pretreated and analyzed using flow cytometry (FACScan, Becton Dickinson). The results were compared with the infiltrate of eosinophils present in the biopsy specimens, which were collected from the distal, middle, and proximal part of esophagus. The largest number of eosinophils observed in the tissue was the one reported in the study. Histological and blood samples were collected simultaneously.

Patients

The study population comprised 43 individuals classified into 4 groups: healthy controls (n=15), allergic patient controls (n=9), active EoE patients (>15 eosinophils present in esophageal biopsy) (n=12), and nonactive EoE patients (n=7). All patients currently or previously classified as having EoE had specific symptoms of EoE, and some of the histopathological studies performed or the current one revealed >15 eosinophils. At the time of the study, none of the 19 EoE patients were being treated with corticosteroids or undergoing treatment with PPIs, although PPIs had been suspended in 4 patients owing to adverse effects. All patients were on a food elimination diet or about to begin one. In patients with EoE, blood samples were obtained simultaneously with the endoscopy for the biopsy specimens. Patients with active EoE presented allergic reactions to grass, olive, cereals, nuts, and eggs, whereas those with inactive EoE had allergy to grass, cow-milk, eggs, nuts, and fish (Table 1). The allergic controls were patients with a recent allergy diagnosis and no previous treatment. They presented with asthma or rhinoconjunctivitis. In addition, patients in the allergy group

Table 1. Demographic Data of Patients and Healthy Controls

	Healthy Controls	Allergic Controls	Active EoE	Nonactive EoE
No.	15	9	12	7
Mean (SD) age, y	40.44 (11.33)	43.00 (19.45)	28.61 (14.25)	26.00 (11.17)
Maximum age	60	70	54	45
Minimum age	18	10	6	15
Male	11 (73.3%)	8 (88.9%)	9 (75.0%)	5 (74.1%)
Female	4 (26.7%)	1 (11.1%)	3 (25.0%)	2 (28.6%)
Allergy	None	Pollen from grasses (55.5%), olive (11.1%), nuts (11.1%), Hymenoptera (22.2%)	Pollen from grasses (38.5%), olive (23.0%), nuts (15.4%), eggs (7.7%), cereals (15.4%)	Pollen from grasses (30.0%), nuts (20.0%), eggs (20%), cow milk (20.0%), fish (10.0%)

had experienced allergic reactions to grass (55.5%), olive (11.1%), Hymenoptera (22.2%), cereals (11.1%), peach (11.1%), and fish (11.1%). Individuals with other diseases or suspected allergy were excluded from the study.

The study was approved by the Ethics Committee of Hospital General Universitario de Ciudad Real, Ciudad Real, Spain in accordance with the Declaration of Helsinki, and the patients signed an informed consent document.

Flow Cytometry

Monoclonal antibodies were used to identify the eosinophils based on flow cytometry. Antihuman Siglec-8 was used to identify the eosinophils in the cytometer, and a series of surface markers were used to identify the active eosinophils (CD69, α subunit of IL-5 receptor [IL5RA], CD44, ICAM-1, and CD63). The eosinophils were identified using both expression of the surface protein Siglec-8 in cell populations and cellular complexity (SSC), as shown in Supplementary Figure 1S. The number of eosinophils analyzed per sample was 500. Expression of the activation markers on the surface of the selected eosinophils was studied using conjugated monoclonal antibodies to calculate the percentage of those that were active. Eosinophils were characterized using the PE-antihuman Siglec-8 antibody and monoclonal mouse IgG1 clone 837535 (R & D Systems). Active eosinophils were characterized using FITC-conjugated monoclonal antibodies against the previously described inducible cell surface proteins, as follows: FITC-anti-human CD69 (monoclonal IgG1, κ, clone FN50), FITC-anti-human IL-5Rα (monoclonal IgG1, clone 26815; R & D Systems, CA, USA), FITC-antihuman CD44 (mouse IgG2b, κ, clone C26), FITC-antihuman-ICAM-1 (mouse IgG1, κ, clone HA58), and FITC-antihuman CD63 (mouse IgG1, κ, clone H5C6) (all FITC-monoclonal antibodies except IL5Rα from BD Biosciences Pharmingen).

Table 2. Absolute Number of Eosinophils in Peripheral Blood

Type of patient	N	Mean (SEM) No. of Eosinophils/μL	Min	Max
Healthy controls	15	320.00 (116.2)	100	1000
Allergic controls	9	266.67 (62.3)	100	700
Active EoE	12	358.33 (82.9)	100	1100
Nonactive EoE	7	300.00 (117.5)	100	800

Statistical Analysis

The statistical analysis was carried out using SPSS Statistics for Windows, Version 21.0 (IBM Corp). The Kruskal-Wallis test was performed to analyze differences in the means of the 4 groups simultaneously for each cell activation marker. Significant results indicate that the 4 groups under study do not behave homogeneously. The Mann-Whitney test was performed by comparing mean differences between 2 groups with respect to each cell marker. The Spearman test was used to verify the correlation between the activation markers and the number of eosinophils present in the biopsy. In order to assess the potential of the activation markers for diagnosis and follow-up, we constructed receiver operating characteristic (ROC) curves based on data from the website of Johns Hopkins University School of Medicine [10], considering 0.5 as no discriminatory capacity and 1 as optimal. Statistical significance was set at $P<.05$. The figures were generated using GraphPad Prism (GraphPad). All results are expressed as mean (SE).

Results

The mean age of the 43 patients analyzed in the present study was 40.44 (11.33) years. Four were children under 12 years. In terms of distribution by sex, 33 were males and 10 females. Table 1 summarizes the demographic data of the 4 groups of patients. The most common IgE-mediated allergies both in the allergic control groups and in patients with EoE (active or inactive) are pollen from grasses and olive and foods such as eggs and nuts (peanuts).

The number of blood eosinophils (expressed as eosinophils/μL) in peripheral blood did not differ between the groups studied. The average number of eosinophils in peripheral blood in each group is shown in Table 2.

The results for the cell markers on the surface of the eosinophil of each group (expressed as percentages) are summarized in Table 3. No significant differences were found for any of the groups studied, except for ICAM-1, whose values were significantly lower in patients with active EoE than in the other groups (Figure 1). Findings for this parameter were similar in the healthy controls, the allergic patients, and patients with stable EoE. The difference in the percentage of blood eosinophils with expression of ICAM-1 between active and nonactive EoE was 39.2% (30.1%) for nonactive patients

Table 3. Results of Surface Activation Markers in Blood Eosinophils of Each Group Studied[a]

Cell Marker	Healthy Controls	Allergic Controls	Active EoE	Inactive EoE	*P*
CD69	24.0 (14.9)	32.3 (24.4)	19.7 (13.3)	22.4 (15.5)	.650
IL5RA	20.0 (14.7)	42.6 (29.4)	22.2 (16.8)	21.8 (15.6)	.902
CD44	53.6 (17.9)	63.4 (26.3)	53.1 (22.4)	47.6 (24.0)	.967
ICAM-1	29.0 (20.2)	39.2 (30.1)	15.7 (7.4)	36.1 (28.4)	.048
CD63	18.4 (13.0)	45.4 (29.1)	24.7 (16.7)	23.4 (13.9)	.967

[a]Results are expressed as percentage of total blood eosinophils (standard error of the mean). The results in the groups were analyzed using the Kruskal-Wallis test.

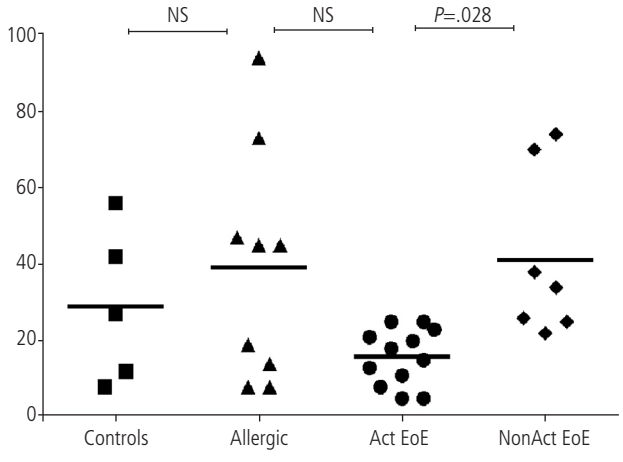

Figure 1. Percentage values for expression of ICAM-1 in blood eosinophils in the 4 groups defined in the study (healthy controls, allergic controls, active EoE patients, and nonactive EoE patients). Patients with active EoE have lower values than the other groups. EoE indicates eosinophilic esophagitis; Act, active; NonAct, nonactive; NS, nonsignificant.

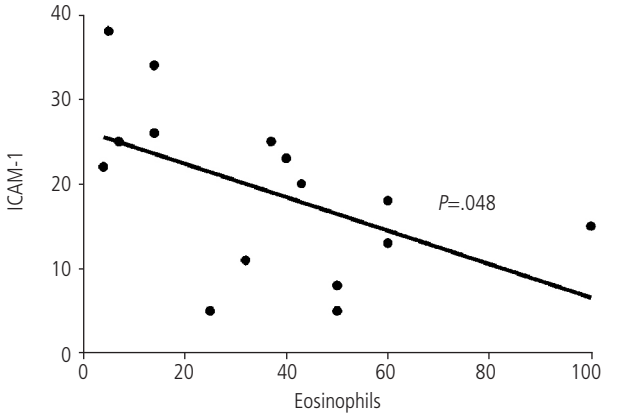

Figure 2. Correlation between the number of eosinophils present in esophageal biopsy specimens and the expression of ICAM-1 in blood eosinophils in 15 patients with EoE.

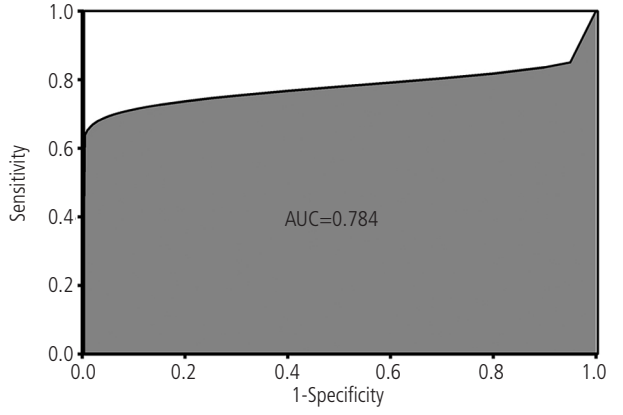

Figure 3. ROC curve analysis of the usefulness of eosinophilic membrane expression of ICAM-1 for discriminating between patients with active EoE and patients without disease activity. AUC indicates area under the curve.

compared with 15.7% (7.3%) for the active EoE patients (*P*=.028) (see Figure 2S Supplementary material for examples of cytometry plots).

Additionally, as shown in Figure 2, an inverse correlation between the number of eosinophils present in the esophageal biopsy and the percentage of ICAM-1 expression in peripheral blood eosinophils was observed in the group of patients with EoE (n=15) (Spearman ρ, –0.501; *P*=.048). All patients belonging to the active EoE group were diagnosed using esophageal biopsy, except for 4 patients, who were diagnosed based only on clinical criteria, without esophageal biopsy data.

Finally, a ROC curve analysis was performed to verify the capacity of the expression of ICAM-1 in eosinophils to discriminate between active EoE and nonactive EoE. The area under the curve for ICAM-1 was 0.784 (Figure 3), in contrast with the other activation markers analyzed, which varied between 0.511 and 0.567. The optimal cut-off point for EoE activity was 21.5% of eosinophils with expression of ICAM-1. Values below this cut-off point indicate disease activity with a sensitivity of 0.75 and a specificity of 0.86.

Discussion

Given the burden of invasive testing with endoscopy and biopsy for diagnosis and monitoring of EoE, a noninvasive, biomarker-based blood test would be of immense value. Recent studies on noninvasive diagnostic methods for EoE analyzed eosinophil degranulation markers from patients' serum. Based on solid-phase sandwich immunoassay, these were found to be elevated in the esophagus of patients with EoE. The authors concluded that there were no significant differences between active and nonactive EoE [1]. In the present study, we analyzed the potential for 5 eosinophil activation markers. Previous studies had shown that the eosinophils present in patients with EoE had a phenotype of activation markers that differed from that of healthy individuals and patients with other diseases [11]. Based on an analysis of surface markers such as CD18, CD44, and CD54 (ICAM-1), a similar study investigated the possible modification of the peripheral blood eosinophil phenotype in patients with active EoE after treatment with corticosteroids. Ishihara et al [12] reported low levels of CD18 on the eosinophil surface, thus leading to poor binding with ICAM-1, although, in contrast with our findings, they did not observe decreased expression of CD54. However, they did observe a decrease in the expression of CD44. This discrepancy in findings can be explained by the fact Ishihara et al did not differentiate between the types of EoE activity, which may vary depending on whether the disease is active or not. In our study, surface marker expression was analyzed using flow cytometry based on unfractionated leukocytes in order to avoid the spurious activation caused by immunomagnetic purification of eosinophils. To date, only peripheral activation of eosinophils based on morphological parameters has been studied; this requires great expertise and is difficult to standardize [13]. Our findings indicate that blood eosinophil phenotypes could be used to identify patients with EoE. Activated eosinophils are effector cells with proinflammatory and destructive capabilities. Eosinophils with activation phenotypes are observed in specimens from the esophagus

of patients with EoE, and deposition of eosinophil products is seen clearly in the affected tissues of these patients [14].

The level of peripheral blood eosinophils holds promise as an EoE biomarker, although the incidence of peripheral blood eosinophilia in EoE patients (defined as >300/μL) might vary and be particularly influenced by factors such as the seasons or concomitant atopic conditions [15,16]. Although a significant correlation between blood eosinophilia and eosinophilic esophageal tissue infiltration has been reported [17], we found that the total number of eosinophils in peripheral blood did not differ between the groups studied. Other studies have also reported a lack of correlation between blood eosinophils and those present in the esophagus [13].

Eosinophils can in turn rapidly upregulate adhesive functionality to bind to an array of counter ligands, potentially leading to further activation of downstream cytoplasmic signaling pathways that influence the cellular responses involved in eosinophil survival and activation [18]. The finding that ICAM-1 expression was decreased in active EoE patients is consistent with the concept that circulating eosinophils are preactivated in EoE. These biological properties of circulating eosinophils may at least partially explain the substantial migration of activated cells into target tissue during acute EoE. Cytokines and chemokines can preactivate eosinophils and increase adhesion molecule expression and cell homing. Several studies in severe asthma report transient or stable downregulation of key adhesion molecules on blood eosinophils, possibly reflecting a high degree of ongoing extravasation in which the eosinophils with the highest expression of activated integrins may be efficiently and continuously removed from the bloodstream [19]. Activation of eosinophils appears to be a reliable indication of what happens when these cells migrate to esophageal tissue. Given their more activated state, eosinophils may degranulate in the target tissue, resulting in esophageal tissue damage in patients with EoE. Induction of ICAM-1 and HLA-DR has previously been reported to be a response to eosinophil-endothelial interaction and is thought to be a consequence of transendothelial migration in general [20]. Other works have also found a negative correlation between active disease and adhesion molecules or chemokine receptors [21].

For the remaining parameters analyzed in the present work, we did not find any differences between the groups studied or between active and nonactive EoE patients. These activation markers may be expressed in the esophagus and mediated by locally produced factors such as periostin, thus facilitating infiltration of eosinophils in the esophagus [22]. Therefore, no changes in their expression in blood eosinophils were observed.

Gastrointestinal endoscopy and histopathology of biopsy specimens are considered the only methods available for diagnosis of EoE, as well as for monitoring the activity of EoE, even though the approach is invasive [23]. Therefore, as a noninvasive method, we propose studying the activity of eosinophils in peripheral blood. Several promising minimally invasive biomarkers for EoE have emerged; however, few are able to differentiate EoE from other atopic diseases. The most commonly reported biomarkers were peripheral blood eosinophils, blood and serum eosinophil granule proteins, and eosinophil surface or intracellular markers [7]. Our and previously reported results reveal a significant difference in the expression of the ICAM-1 marker between patients with active and nonactive EoE. Expression of this marker is decreased in patients with active EoE.

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Conflicts of Interest

The authors declare that they have no conflicts of interest.

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