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Rhinitis: Is It Beyond a Local Inflammation?

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Abbreviations: LMR: Lymphocyte To Monocyte Ratio; MLR:

ABSTRACT

Objective: Rhinitis affects most of the population and its economic burden is serious. Even though it is the local inflammation of the nasal mucosa with Allergic (AR) Or Non-Allergic (NAR) mechanisms, it is not known whether it causes systemic inflammation which can increase the morbidity and mortality. In this study, we aimed to investigate the systemic inflammation in patients with chronic rhinitis using novel serum inflammation markers. Therewith, we would answer if these parameters have an effect on determining various endotypes.

Methods: In this retrospective case-control study, we included 436 patients with newly diagnosed AR (n:179), NAR (n:157), and 103 healthy individuals. Inflammation related blood parameters were collected as Lymphocyte/Monocyte Ratio (LMR), Neutrophil/Lymphocyte Ratio (NLR), Eosinophil/Neutrophil Ratio (ELR), and Systemic Immune Inflammation Index (SII).

Results: All groups were similar in terms of age, gender, or body mass index. Neutrophil counts were significantly higher both in AR and NAR groups compared to controls (4.51 ± 0.09, 4.54 ± 0.1 *vs.* 3.73 ± 0.1, p<0.001). NLR (1.91 ± 0.56, 1.89 ± 0.61, 1.61 ± 0.59, p<0.001), LMR (5.76 ± 0.17, 5.93 ± 0.17, 5.1 ± 0.15, p=0.005), ELR (0.1335 ± 0.007, 0.0999 ± 0.006, 0.12 ± 0.009, p=0.003), SII (533.3 ± 16.6, 558.1 ± 20.9, 479.9 ± 22.2, p=0.035), and CRP (1.44 ± 0.09, 1.67 ± 0.09, 0.87 ± 0.04, p<0.001) were significantly higher in AR and NAR groups than the controls, respectively. SII (r=0.146, p=0.007) and ELR (r=0.254, p<0.001) was significantly correlated with presence of asthma.

Conclusion: We found that systemic circulation of inflammatory cells was significantly increased in patients with/without allergy compared to the control group. This study showed that not only AR, but also NAR triggers a systemic increase of inflammation which supports the link between rhinitis and comorbid conditions such as asthma, chronic hyperplastic eosinophilic sinusitis, nasal polyposis, and serous otitis media. Therefore, effective treatment is suggested for both local inflammation and its systemic manifestations.

Neutrophil To Lymphocyte Ratio; ELR: Eosinophil To Lymphocyte Ratio; SII: Systemic Immune Inflammation Index; CRP: C-Reactive Protein; MPV: Mean Platelet Volume; PLR: Platelet to Lymphocyte Ratio

INTRODUCTION

Inflammation of the nasal lining membranes characterized by nasal symptoms such as itching, rhinorrhea and/or nasal congestion is defined as rhinitis. Rhinitis is a common pathological condition with morbidity associated with a significant financial burden on healthcare systems [1]. The three most commonly accepted subgroups of rhinitis so far are Allergic Rhinitis (AR), infectious rhinitis, and non-allergic Non-Infectious Rhinitis (NAR) [2]. However, these phenotypes may overlap in many patients and are not always easy to distinguish from each other. Due to the diversity of pathophysiological mechanisms and clinical symptoms, it is difficult to develop clear guidelines for diagnosis and treatment [3].

The presence of local nasal inflammation may progress to some changes in the periphery, rationalizing it may provide some convenience. It has been well known that Allergic Rhinitis (AR) triggers a systemic increase of inflammation, within minutes of allergen exposure. Increase in systemic circulation of inflammatory cells results to their infiltration into other tissues and to development of comorbid conditions such as asthma, sinusitis, and nasal polyposis [1]. Even though these comorbidities are as frequent in Non-Allergic Rhinitis (NAR) as in AR, systemic inflammation is not well studied. The best known on this subject is that rhinitis is sometimes accompanied by high eosinophils with no details about other inflammatory cells in the blood in some NAR patients. Although position papers recommend distinguishing NAR from infectious rhinitis and local AR, the differences about the definition of NAR in studies makes difficult to discuss the results. In order to evaluate systemic inflammation recently, attention has been focused on predicting the course of the disease using minimally invasive methods such as blood sampling. Numerous studies have reported that Neutrophil-Lymphocyte Ratio (NLR), Lymphocyte-Monocyte Ratio (LMR), Platelet-Lymphocyte Ratio (PLR) and Eosinophil-Lymphocyte Ratio (ELR) can be used as inflammatory markers in chronic inflammatory diseases.4 Although various studies have been carried out on peripheral blood sampling regarding endo-typing in patients with and without polyps, as well as in patients with allergic rhinitis, as far as we know, no study has been conducted under the umbrella of rhinitis, including the systemic immune inflammation index. The rationale of this study is that, there is almost no study showing systemic inflammation by inflammatory blood cells in AR or NAR which has been suggested that these phenotypes have different inflammatory profiles [5]. Determining systemic inflammation by using objective parameters may facilitate the implementation of special medical treatments to risky patients. We hypotheses that there is an increase in SII in both AR and NAR. The primary aim of this study was to determine whether systemic inflammation could be determined in rhinitis by using new inflammatory markers such as NLR, LMR, PLR, ELR and SII. Our secondary aim was to compare systemic inflammation in rhinitis phenotypes as AR and NAR.

MATERIALS AND METHODS

The study was conducted at the Department of Allergy and Clinical Immunology of a tertiary teaching hospital. Data of rhinitis patients collected between January 2017 and 2022 were analyzed retrospectively. Ethics committee

approval was received from the chair of the local clinical ethics committee of the Kirikkale University Medical Faculty (2021.02.04, 2021/05). This study was performed according to the Declaration of Helsinki II [4,5].

Study groups

To be eligible for participation, patients had to meet the following inclusion criteria: age between 16 and ≤ 65 years; persistent/intermittent rhinitis with or without asthma. Patients with pregnancy or breastfeeding, under 16 and over 65 ages, which have systemic diseases, such as parasitic disease, having collagen vascular disease, allergic bronchopulmonary aspergillosis, Churg–Straus syndrome, drug use that may affect peripheral blood parameters (systemic corticosteroid etc.), blood malignancies, and any active systemic inflammation condition were excluded from the study. Healthcare personnel who underwent annual medical check-up during the study period acted as the control group; however, those with any chronic diseases or active infections were excluded.

Diagnosis of rhinitis and asthma

Rhinitis was diagnosed by allergy specialists if the patient had at least two symptoms of nasal itching, obstruction, rhinorrea and sneezing at least for one hour and two consecutive days. Asthma was diagnosed according to asthma guideline as variable airway symptoms and reversible airway obstruction in pulmonary function test [6]. Patients with asthma were enrolled only if they were under regular low dose inhaled corticosteroid treatment (budesonid or equivalent <400 mcg/day) and had well-controlled asthma due to Asthma Control Test scores (ACT ≥ 20).

Allergy tests

Skin Prick Tests (SPT) were performed using standard commercially available allergen extracts (grasses mix, cereals mix, dermatophagoides (D) pteronyssinus, D. farinae, blatella, cat epithelia, dog epithelia, *Aspergillus fumigatus*, alternaria, clodosporium, *Artemisia vulgaris*, *Parietaria officinalis*, ALK-Abello/Madrid). The skin test allergen panel has been created according to the prevailing geographical and climatic conditions. SPT were performed on both forearms in accordance with international guidelines. Histamine (10 mg/mL) was used as a positive control, and sterile saline 0.09% as a negative control. A wheal diameter of ≥ 3 mm, greater than the negative control, was considered as a positive prick test [7]. Serum specific immunoglobulin (Ig) E was analysed (UniCAP 100-Pharmacia, positive: ≥ 0.35 kU/L) against to aeroallergens (house dust mites, grass/cereal pollen mix, blatella, cat, dog, mold mix). Patients with a positive SPT and/or specific IgE against to aeroallergens defined as AR if their symptoms were relevant with the allergy tests. NAR was diagnosed if there was no allergen triggering and negativity in SPT and specific IgE.

Computerized tomography

Patients who had rhinitis complaints and had paranasal tomography were included in the study. The diagnosis of nasal polyposis according to the European position paper on rhinosinusitis and nasal polyps consensus depends on the presence of two or more nasal symptoms one of which should be either nasal blockage or nasal discharge and/or reduction/loss of smell, and/or facial pain for more than 12 weeks, and the presence of either nasal polyps and/or paranasal sinusitis by Computed Tomography (CT) scan [8,9]. Those with AR and polyps on CT were classified as ARwNP, and without polyps were classified as ARwoNP. Those with NAR and polyps on tomography were classified as NARwNP, and without polyps were classified as NARwoNP.

Laboratory features

CBCs were obtained from all patients. Blood samples were taken from the patients and placed into tubes containing calcium EDTA (ethylenediaminetetraacetic acid) for use in an automated blood counter device. NLR, ELR, PLR, LMR and SII (SII formula=neutrophils × platelets/ lymphocytes count) were calculated from the CBC. The

CBCs had automated differential counts, measured and showed total WBC, neutrophil, eosinophil and lymphocyte counts per microliter. The LMR, NLR, PLR and ELR were calculated due to formulas.

Statistical analysis

Statistical analysis was conducted using SPSS software version 22.0 (SPSS, Inc., Chicago, Illinois). Variables were analyzed using visual and analytical methods to determine if they were normally distributed. Mean and standard deviation or median and interquartile ranges were used for descriptive statistics, also number and % were used for categorical variables. Chi-square test was used to compare nominal and categorical variables. Parametric data were compared using T-test and non-parametric data with Mann–Whitney U test. We used One-way ANOVA test for comparing more than two groups with parametric distribution and Kruskal Wallis test for non-parametric variables. Post hoc tests (Tamhane and Tukey test) were used to determine the significant difference between the groups. A two-sided $p<0.05$ was considered statistically significant. Spearman test for abnormally distributed and Pearson test was used for parametric parameters in correlation analysis. The correlation coefficient (R value) and p value were determined.

RESULTS

In this study 2489 patients were screened and 2153 patients were excluded according to the exclusion criteria. In our study, 336 rhinitis patients were evaluated. There was no significant difference between the groups in terms of baseline demographic variables. We determined that 31 individuals in the AR group and 26 individuals in the NAR group were diagnosed with asthma. We determined that there were significant differences in the values of AR and NAR groups compared to the control group (eosinophil, monocyte, SII, LMR, ELR, CRP and NLR). Comparison and analysis of AR and NAR groups are presented in Table 1.

Table 1. Baseline demographic and laboratory parameters of study groups.

Parameters	AR (n=179)	NAR (n=157)	Control (n=103)	p-Value
Age	33.6 ± 0.8	35.8 ± 0.8	36.1 ± 0.6	0.071
Sex, n Female	98	87	50	0.491
Male	81	70	53	
BMI, kg/m^2	30.9 ± 0.2	31.3 ± 0.2	31.1 ± 0.3	0.514
Asthma, n-%	31, 17.3%	26, 16%	-	0.752
Platelet, (10^3/µL)	280.5 ± 4.7	292.2 ± 5.3	296.2 ± 7.2	0.103
MPV	10.2 ± 0.08	10.1 ± 0.07	9.39 ± 0.12	0.06
Eosinophil (10^3/µL)	0.338 ± 0.02	0.234 ± 0.01	0.278 ± 0.02	<0.001***
Neutrophil (10^3/µL)	4.51 ± 0.09	4.54 ± 0.1	3.73 ± 0.1	<0.001#
Lymphocyte (10^3/µL)	2.54 ± 0.06	2.56 ± 0.05	2.47 ± 0.06	0.677
Basophil (10^3/µL)	0.0436 ± 0.004	0.0387 ± 0.002	0.0385 ± 0.002	0.554
Monocyte (10^3/µL)	0.472 ± 0.01	0.457 ± 0.01	0.511 ± 0.01	0.008**
SII	533.3 ± 16.6	558.1 ± 20.9	479.9 ± 22.2	0.035**
LMR	5.76 ± 0.17	5.93 ± 0.17	5.1 ± 0.15	0.005#
CRP, mg/dl	1.44 ± 0.09	1.67 ± 0.09	0.87 ± 0.04	<0.001##
NLR	1.91 ± 0.56	1.89 ± 0.61	1.61 ± 0.59	0.002#
PLR	118.8 ± 2.7	122.07 ± 3.2	130.4 ± 5.3	0.092
ELR	0.1335 ± 0.007	0.0999 ± 0.006	0.12 ± 0.009	0.003***
Groups with significant difference: * : AR-Control, **: NAR-Control, ***: AR-NAR, # :Control-AR and NAR, ##: All groups; p-value <0.05 was considered statistically significant.				

We compared rhinitis patients according to the presence and absence of polyps. We found that asthma was higher in those with polyps. Significant differences were found between the new inflammation markers of the groups and their comparison is presented in Figure 1. The comparison of the groups according to the presence of polyps is presented in Table 2.

Figure 1. Comparison of NLR and LMR parameters between AR and NAR groups according to the presence of polyps. **Note:** : LMR; : NLR.

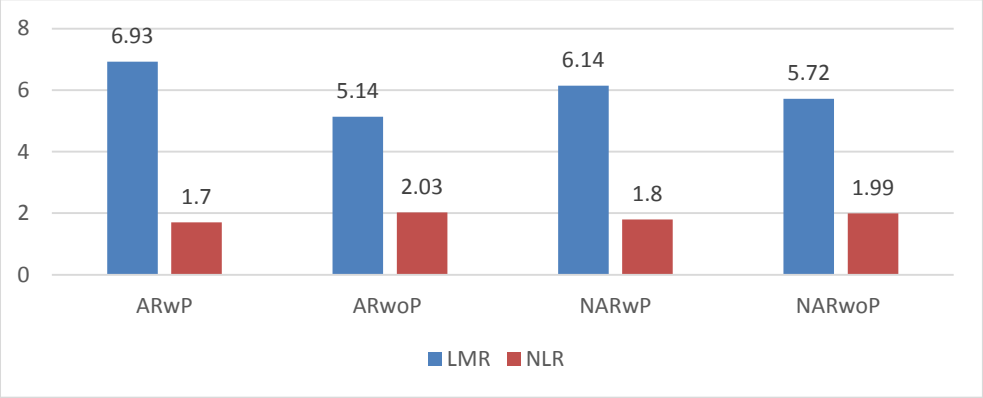

Table 2. Comparison of AR-NAR groups with and without nasal polyps.

Parameters	ARwP (n=62)	ARwoP (n=117)	NARwP (n=79)	NARwoP (n=78)	P-Value
Asthma, n- %	14, 22%	17, 14.5%	23, 29%	3, 3.8%	<0.001*
Platelet, (10^3/µL)	296.5 ± 10.2	271.6 ± 4.6	310.4 ± 8.1	273.9 ± 6.4	<0.001*
MPV	10.6 ± 0.12	10.08 ± 0.09	10.1 ± 0.1	10.1 ± 0.1	0.001*
Eosinophil (10^3/µL)	0.419 ± 0.03	0.255 ± 0.02	0.219 ± 0.02	0.242 ± 0.01	<0.001*
Neutrophil (10^3/µL)	4.59 ± 0.13	4.47 ± 0.12	4.55 ± 0.15	4.53 ± 0.15	0.947
Lymphocyte (10^3/µL)	2.96 ± 0.12	2.32 ± 0.06	2.72 ± 0.08	2.40 ± 0.07	<0.001*
Basophil (10^3/µL)	0.0414 ± 0.007	0.0447 ± 0.006	0.0413 ± 0.003	0.0361 ± 0.003	0.733
Monocyte (10^3/µL)	0.459 ± 0.01	0.479 ± 0.01	0.471 ± 0.01	0.444 ± 0.01	0.35
SII	503.8 ± 27.5	548.9 ± 20.7	568.3 ± 32.5	547.8 ± 26.3	0.464
LMR	6.93 ± 0.35	5.14 ± 0.15	6.14 ± 0.25	5.72 ± 0.23	<0.001*
CRP, mg/dl	1.51 ± 0.16	1.4 ± 0.12	1.49 ± 0.12	1.86 ± 0.15	0.097
PLR	110.6 ± 5.6	123.1 ± 2.9	122.6 ± 4.8	121.4 ± 4.3	0.183
NLR	1.7 ± 0.08	2.03 ± 0.07	1.8 ± 0.09	1.99 ± 0.08	0.017*
ELR	0.1584 ± 0.01	0.1084 ± 0.009	0.835 ± 0.01	0.1086 ± 0.07	<0.001*
Groups with significant difference: NLR: ARwP-ARwoP, LMR: ARwP-ARwoP, ARwP-NARwoP, ARwoP-NARwP, ELR: Lymphocyte: ARwP-ARwoP, ARwP-NARwoP, ARwoP-NARwP, Platelet: ARwoP-NARwP, NARwP-NARwoP, MPV: ARwP-ARwoP, ARwP-NARwP, Eosinophil: ARwP-ARwoP, ARwoP-NARwP, NARwP-NARwo.*p-value <0.05 was considered statistically significant.					

In the correlation analysis, pollen and weed allergy was correlated with polysensitization. LM score, ELR and SII values of asthmatic patients were positively correlated. All the variables that were significant in the correlation analysis are presented in Table 3.

Table 3. Correlation analysis of the variables included in the study.

Variables		R-value	P-value
Mite	Polisens	0.157	0.004
	Monocyte	0.118	0.031
	MPV	0.171	0.002
Polen	Polisens	0.621	<0.001
	Eosinophil	0.169	0.002
	ELR	0.125	0.022
Weed	Polisens	0.635	<0.001
	LM score	-0.277	<0.001
Cat	LM score	-0.152	0.031
	Polisens	0.245	<0.001
Dog	Polisens	0.242	<0.001
Asthma	LM score	0.362	<0.001
	IgE	0.462	0.008
	Monocyte	0.121	0.027
	Platelet	0.132	0.015
	Eosinophil	0.282	<0.001
	SII	0.146	0.007
	ELR	0.254	<0.001

DISCUSSION

Rhinitis is a common condition caused by inflammatary process and incidence is increasing. Abnormal immune response and inflammatory course may play an important role in the pathogenesis of rhinitis, but our knowledge on this subject is limited. In our study, inflammatory markers in rhinitis were evaluated. We determined that there were significant increases in SII, LMR, NLR and hs-CRP measurements, which are indicators of systemic inflammation, in the rhinitis group compared to the control group. In addition, asthma was observed more frequently in patients with rhinitis with polyps than in patients without polyps.

In recent times, many parameters obtained from blood have been reported to be associated with systemic inflammation. Neutrophil-to-lymphocyte ratio is the most frequently investigated and best known parameter among these. NLR has proven its prognostic value in cardiovascular diseases, inflammatory diseases, cancers and in many different diseases [10]. In study of Dogru, et al., 438 pediatric patients were examined and NLR was found to be significantly higher in the AR group compared to the control [11]. In another study conducted in adults, it was reported that NLR was significantly higher in AR patients similar to our results [12]. In another study, it was shown that NLR value decreased significantly after follow-up in patients with chronic rhinosinositis with polyps treated with Endoscopic Sinus Surgery (ESS) and nasal mometasone furoate [13]. Our study showed that the NLR mean of the control group was similar to the mean reported in healthy individuals and rhinitis patients have a significantly higher NLR value. This elevation was mostly associated with a significant increase in neutrophil values. However, the NLR value of the group without polyps was significantly higher in the AR group compared to the ARwP group. Although there are many studies evaluating allergic rhinitis, it seems that there is still no study including the NAR group. Our study is the first to evaluate all rhinitis patients. In our study, we determined that the systemic inflammatory markers NLR of both AR and NAR groups were significantly higher. Since NLR is associated with

increased disease severity and mortality risk, we think that this increase may have important consequences in patients with rhinitis, which is common in the community. Rhinitis is characterized by chronic inflammation of the nasal mucosa. In AR patients, T-helper 2 lymphocytes, neutrophils and eosinophils play an active role during the late phase immune response after allergen exposure [14]. In previous studies, both local and systemic increased eosinophil levels have been reported in AR patients [15]. In a study which patients with nasal polyps were evaluated by biopsy, high numbers of activated eosinophils, neutrophils and plasma cells were reported in nasal polyps [16]. Lavinskieneve, et al. showed that neutrophils are important cells in the reaction caused by late-phase allergy in allergic airway diseases, their number and activity increase, and therefore activated peripheral blood neutrophils are guiding the inflammatory processes [17]. In our study, serum eosinophil values were higher in the AR group compared to the other groups. Again, neutrophil count which plays an important role in pathogenesis was higher in rhinitis patients compared to controls, but there was no difference between AR and NAR groups. These findings provide important information about the role of neutrophil in the pathogenesis of rhinitis. The data of our study show that inflammation in rhinitis patients is not only local and causes changes in systemic circulation measurements.

Eosinophil-to-lymphocyte ratio is an important parameter that reports increased inflammation especially in allergic conditions, and its use has been increasing in recent years. Significant elevations in allergic rhinitis were reported in studies in both children and adults compared to control patients [18,19]. In Takahashi, et al. study, rhinitis patients with asthma were found to have significantly higher eosinophil and IgE levels compared to the non-asthmatic group [20]. In our study, we determined that there was a significant ELR value in AR patients compared to other groups, similar to the literature. It is known that inflammatory processes play an important role in the pathophysiology of nasal polyps, which is another important problem in rhinitis, and we can say that this inflammation was reflected in systemic circulation measurements in our study. We determined that eosinophil and ELR elevation were highest especially in the ARwP group. In addition to the literature, our study showed that ELR increased much more in the AR group with polyps. Additionally in the correlation analysis, we determined that there was a positive significant relationship with the presence of asthma. These data suggest that ELR may indicate the presence of polyps in AR patients and may be associated with asthma.

It is known that the pathophysiology of rhinitis is multifaceted and includes heterogeneous groups. It has been reported in many studies that the systemic immune-inflammation index and LMR can be used as an indicator of increased systemic inflammation in different disease groups and can be a prognostic marker various diseases [21,22]. In the literature, we could not find a study in which these parameters were evaluated in both AR and NAR patients. In a study evaluating patients with chronic rhinosinusitis, it was reported that neutrophil, monocyte and eosinophil counts, as well as CRP, NLR and MLR were significantly higher in patients with polyps [23]. In another study, Sivrice, et al. showed that the systemic immune inflammation index can be used to predict preoperative nasal polyp subtypes [24].

CONCLUSION

Although rhinitis patients are evaluated in different subgroups, we can say that they may have similar pathophysiological processes. In our study, we determined that SII and LMR values were significantly higher in rhinitis patients compared to controls. In addition, the LMR value was even higher in those with polyps in both the AR and NAR groups. Our results suggest that initial assessments of rhinitis patients could benefit from analysis of inflammation-based markers obtained by CBC. High levels of inflammation-based markers can guide the clinician in earlier treatment planning.

LIMITATIONS

An important limitation is that measurements such as NLR, LMR and SII are affected by several different states and are not specific. Another limitation was the relatively small number of patients included in our study. Although the same measurement method was used in our study, different values between measurements in different units may be encountered and this seems to cause an important standardization problem.

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