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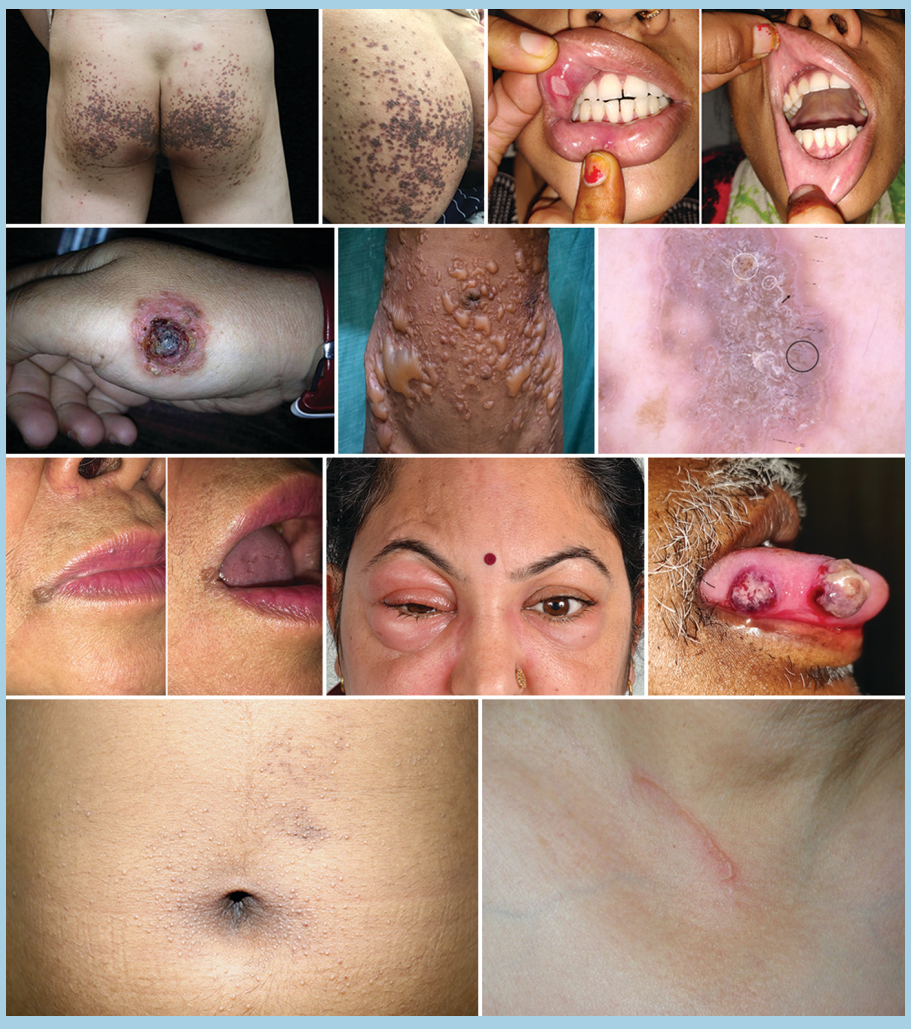

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ORIGINAL ARTICLE

Do Platelet Count and mean Platelet Volume have a Predictive Role as a Marker in Children with Atopic Dermatitis?

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Abstract

Background: It is known that platelets play an important role in inflammatory diseases. Atopic dermatitis (AD) is a chronic, itchy, recurrent inflammatory skin disease that affects 2%-30% of the population, especially in childhood. **Aims:** We investigated the role of platelet count and mean platelet volume (MPV) as biomarkers in children with AD. **Methods:** This cross-sectional retrospective study examined the medical reports of patients who were referred to the Pediatric Allergy and Immunology Outpatient Clinic of the Medical Faculty Hospital, Istanbul Biruni University and the Pediatric Immunology and Allergy Diseases Outpatient Clinics of the Izmir S.B.U Tepecik Training and Research Hospital, for AD. A total of 167 children with AD and 170 healthy children were included in the study. **Results:** Among all participants, 36.5% (n = 61) and 31.8% (n = 54) were female in the patient and control groups, respectively. The mean age was 2.8 ± 2.8 and 3.3 ± 2.5 years in the patient and control groups, respectively. MPV was statistically significantly higher in the patient group than in the control group (P =0.003). Mean platelet to neutrophil ratio and mean absolute lymphocyte count values were significantly higher in the patient group (P <.0001 for both values). However, the mean absolute neutrophil count was lower in the patient group than in the control group and it was considered statistically significant (P <.0001). **Conclusion:** In conclusion, we found significantly higher platelet counts in patients with AD. The decrease in the neutrophil to lymphocyte ratio rate was remarkable. However, there was no significant difference in the MPV values between the patient and control groups.

Key Words: *Atopic dermatitis, eczema, mean platelet volume, platelet count, thrombocytosis*

Introduction

Platelets are produced from megakaryocytes that differentiate in the bone marrow. Thrombopoiesis is induced through thrombopoietin. Their lifespan in the bloodstream is approximately 7-10 days.[1] They can synthesize a limited number of proteins via mRNA because they do not have nuclei. Platelets are discoid-shaped cells at rest.[2] Platelets play a very important role in hemostasis, vasoconstriction, and tissue repair and in the inflammatory process. Activated platelets discharge their granules out of the cell during the inflammation process.[3-5]

Atopic dermatitis (AD) is a common chronic allergic skin disease in children. Although its pathophysiology is complex, it occurs as a result of genetic, immunological, and environmental factors, especially epithelial barrier dysfunction. Many cellular elements such as epithelial cells, keratinocytes, antigen presenting cells, lymphocytes, mast cells, eosinophils, and native lymphoid cells play a role in the pathogenesis of AD. T helper 2 (Th2) cell differentiation is triggered by the effect of alarmins (IL-25, IL-33, and Thymic stromal lymphopoietin) produced from epithelial cells. While there is Th2 dominance in the early period, in the chronic phase other lymphocyte subgroups and the cytokines it produces are functional together with Th2. Overall, there are many cellular elements and cytokines and mediators secreted from these cells are involved in the pathophysiology of AD.[6,7] We consider that together with these immune system elements, platelets also play an active role in AD. In clinical studies, platelets' role has been demonstrated in many inflammatory diseases.[8,9] Likewise, it is known that mean platelet volume (MPV) tends to increase or decrease during

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the inflammatory process.[8-11] When activated, the cytoskeleton is rearranged through microfilaments. Thus, it first transforms to a spherical shape from a disc shape and then turns in to a form in which the cell membrane becomes more spreading and protruding.[2] Accordingly, MPV has been evaluated in different patient groups such as those with rheumatologic, autoimmune, infection, and cardiovascular diseases.[12,13] Although there are some studies evaluating the relationship between allergic diseases and MPV in adults, these data are limited in the pediatric age group. In our study, we aimed to evaluate platelet count (TC) and MPV in children with AD.

Materials and Methods

This cross-sectional retrospective study examined the medical records of the patients who were referred to the Pediatric Allergy and Immunology Outpatient Clinic of the Medical Faculty Hospital, Istanbul Biruni University and the Pediatric Immunology and Allergy Diseases Outpatient Clinics of the Izmir S.B.U. Tepecik Training and Research Hospital for AD. The study was approved by the Institutional Ethical Committee of the Biruni University.

Patients

We reviewed the medical records of the patients presented to our hospital and diagnosed with AD between January 2022 and July 2022. The diagnosis of AD was confirmed as per the Hanifin Rajka Criteria.[14] Patients with incomplete data; who did not have a complete blood count at presentation; who had a concomitant chronic inflammatory skin disease; who developed primary and/or secondary skin infections; and who had a clinical infection at the time of presentation and/or who received antibiotherapy were excluded. We also excluded those with iron deficiency anemia at presentation or during follow-up or who received treatment for iron deficiency. Otherwise, all children aged 0 to 18 years with a diagnosis of AD were included in the study. As a result, the patient group consisted of a total of 167 patients. Also, 170 healthy children of equivalent age and gender were randomized as the control group. We compared the same parameters between the patient and control groups.

Data evaluation

Demographic data, gender, age, blood tests, total IgE levels, skin prick test results, and SCORAD symptom score showing the severity of AD were retrieved from patients' medical records. Blood samples for the complete blood count (CBC) were analyzed by XT-1800i using EDTA as the anticoagulant. Among the CBC results, absolute lymphocyte count (ALC), absolute eosinophil count (AEC), absolute neutrophil count (ANC), TC, MPV, hemoglobin (Hb), and erythrocyte (RBC) values were recorded for each patient. The neutrophil to lymphocyte ratio (NLR) was calculated by dividing the ANC by the ALC. The platelet to neutrophil ratio (PNR) was calculated by dividing the platelet count by the ANC. Patients with a SCORAD index below 25 were considered "mild," between 25 and 50 "moderate," and above 25 "severe". The results of the specific IgE, skin prick test performed for food, or aeroallergen sensitivity were analyzed. Food-specific IgE values less than 0.35 kUA/l were considered negative. Skin prick tests were performed on the volar forearm, face, or back of the patients. Systemic antihistamines were discontinued 1 week prior to the skin prick test. For skin prick tests, histamine was used as a positive control and physiological saline was used as a negative control. The reactions were read 15 minutes after application. Allergens that produced an induration at least 3 mm greater than that of the negative control (excluding erythema) were considered positive, while those less than 3 mm were considered negative.

Statistical analysis

Data were analyzed using the SPSS statistical software, version 22 (SPSS Inc, Chicago, IL). Continuous variables were expressed as mean ± SD and categorical variables as number (%). For comparisons, we used independent *t*-test and one-way ANOVA test for continuous variables and Chi-squared test for categorical variables. Pearson's test was used for correlation analysis. P <.05 was considered statistically significant.

Results

Overall, 36.5% (n = 61) of the 167 patients and 31.8% (n = 54) of the control group were female. The mean age was 2.8 ± 2.8 and 3.3 ± 2.5 years in the patient and control groups, respectively. There was no significant difference between the two groups in age and gender. Comparison of demographic and laboratory results of the two groups is shown in Table 1. The mean platelet count of the patient group was statistically significantly higher than in the control group (P =0.003). Mean PNR and mean ALC values were significantly higher in the patient group (P <.0001 for both values). However, the mean ANC of the patient group was lower than in the control group and it was considered statistically significant (P <.0001). The patients were divided into three groups as per the SCORAD index: mild (116 patients), moderate (41 patients), and severe (10 patients). A comparison of mild, moderate, and severe patients is shown in Table 2. There was no statistical difference among the three groups in terms of age and gender. Significant differences were observed in mean TC, AEC, and ALC values (P <.0001 for all three parameters). The mean TC of patients with moderate eczema was higher than those with mild eczema, with a statistically significant difference (P <.001). A comparison of the moderate and severe eczemas for mean ALC

Table 1: Comparison of study groups

	Patients (*n*=167)	Control (*n*=170)	*P*
Gender			
Female (*n*, %)	61 (36.5%)	54 (31.8%)	0.35
Male (*n*, %)	106 (63.5%)	116 (68.2%)	
Age (years, mean±SD)	2.8±2.9	3.3±2.5	0.136
Platelet (count/mm^3, mean±SD)	430874.25±3.1	356311.76±1.1	0.003
MPV (femtoliter, mean±SD)	8.6±1.1	8.6±0.67	0.613
NLR (ratio, mean±SD)	0.84±1.4	2.05±2.3	< 0.0001
PNR (ratio, mean±SD)	179.6±162.7	97.7±72.4	< 0.0001
Lymphocyte (count/mm^3, mean±SD)	5232.4±2260.5	3997.1±1911	< 0.0001
Neutrophil (count/mm^3, mean±SD)	3725±8352.4	5510±3641.2	0.011
Eosinophil (count/mm^3, mean±SD)	498.1±575.7	144.4±212.3	< 0.0001
Eritrocyte (million/microliter, mean±SD)	4.6±0.6	4.6±0.3	0.249
Hemoglobin (grams/deciliter, mean±SD)	11.9±0.8	12.1±1.1	0.08

MPV, mean platelet volume; NLR, Neutrophil to lymphocyte ratio; PNR, Platelet to neutrophil ratio

and AEC showed that severe cases had higher ALC and AEC values and there was a statistically significant difference (*P* <.0001 for both parameters). The AEC value of the patients with severe eczema was statistically higher compared to the mild cases (*P* <.0001). When the patient group was evaluated between those with and without allergen sensitization, 71 cases had allergen sensitization [Table 3]. Six patients were sensitive to aeroallergens and 65 patients were sensitive to food allergens. Between these two groups, the mean ALC and AEC values of patients with allergen sensitization were higher, with a statistically significant difference (*P* <.0001 and *P* =0.008, respectively). However, there was no difference between mean platelet counts, MPV, NLR, and PNR. When the correlation between the SCORAD index and other laboratory parameters was evaluated, a positive correlation was found for TC and AEC (r = 0.293 *P* <.0001 and r = 0.420 *P* <.0001, respectively).

Discussion

The role of platelets in allergic inflammation has been known for many years. It has been demonstrated that the activation, number, and MPV value of platelets change in many allergic diseases.[15] When platelets are activated in inflammation, they undergo a change in shape.[16,17] Akelma AZ *et al*.[18] showed that MPV value decreased significantly in 40 patients with chronic spontaneous urticaria compared to the control group. In some studies with asthmatic patients, no significant difference was found in MPV, while in others, MPV was statistically significantly lower.[15,19,20] It is difficult to make a conclusion regarding the MPV value in patients with AD at present as two different studies examining MPV in AD cases showed contradictory results.[21,22] In our study, mean MPV values of the patient and control groups were very close to each other and there was no significant difference. Similarly, MPV value in patients with mild, moderate, and severe AD were similar to each other. No difference was found between the patient group with and without allergen sensitization.

In inflammation, platelets are activated and work in coordination with both adaptive and innate immune system elements. In literature, there are studies examining TC in respiratory tract allergy diseases and skin allergies. Nacaroglu HT *et al*.[20] found thrombocyte counts to be higher in asthma patients compared to the control group, with a significant difference. In this study, there was no difference in mean TC between asthmatic patients at the time of attack and those who were asymptomatic. Our patients with AD had statistically high mean platelet counts and had a positive correlation with the SCORAD index. TC was significantly higher in patients with severe and moderate AD than those with mild AD [Table 2]. In addition, TC can be a guide when evaluating the severity of eczema in the near future and it can be used as a criterion so that it can provide practical benefits with a simple blood test when investigating patients. As per our results, TC values more than 570.000/mm^3 were found to be remarkable in moderate and severe eczema.

Platelets play an important role in the activation, adhesion, transmigration, and chemotaxis of leukocytes.[1,15] Therefore, we wanted to evaluate NLR and PNR in our study. The mean ALC and AEC values were statistically significantly higher in the patient group than in the control group. However, the mean ANC was higher in the control group. While NLR was lower in the patient group, PNR was significantly higher. NLR has been evaluated in many patient groups. NLR increase has been established in many infectious diseases, neonatal sepsis cases, and rheumatic diseases.[23,24] In recent studies, no significant difference was found in NLR between the AD patients and the control group.[21,25] NLR was significantly lower in patients with AD in our study. When compared as per the SCORAD index and the allergen sensitization, NLR was lower in patients with mild eczema and nonsensitized eczema. However, there was no statistically significant difference between these groups. NLR has been shown to be significantly higher in patients with Stevens-Johnson syndrome.[26] However, it was significantly lower in patients with AD in our study. It might be associated with the fact that neutrophils are dominant in Stevens-Johnson syndrome, while lymphocytes are dominant in AD. It has been shown

Table 2: Comparison of patient groups according to SCORAD index

	Mild (*n*=116)	Moderate (*n*=41)	Severe (*n*=10)	*P*
Gender				
Female (*n*, %)	46 (39.7%)	13 (31.7%)	2 (20%)	0.354
Male (*n*, %)	70 (60.3%)	28 (68.3%)	8 (80%)	
Age (years, mean±SD)	3.1±3.3	2.4±1.8	1.6±1.07	0.166
Platelet (count/mm^3, mean±SD)	367896.5±1.1	570170±5.6	590300.1±1.4	< 0.0001*
MPV (femtoliter, mean±SD)	8.6±1.1	8.6±1.1	8.9±0.6	0.736
NLR (ratio, mean±SD)	0.9±1.7	0.7±0.8	0.3±0.2	0.512
PNR (ratio, mean±SD)	162.8±147.1	213.1±207.2	236.4±93.8	0.123
Lymphocyte (count/mm^3, mean±SD)	4929.7±2184.5	5455.5±2196.7	7829±1709	< 0.0001*
Neutrophil (count/mm^3, mean±SD)	3818.6±9859.6	3656.9±3064.2	2919±1405.9	0.947
Eosinophil (count/mm^3, mean±SD)	408.4±411.9	422.4±406.5	1841±1029.2	< 0.0001*
Eritrocyte (million/microliter, mean±SD)	4.6±0.6	4.6±0.4	4.8±0.3	0.683
Hemoglobin (grams/deciliter, mean±SD)	12±0.8	11.8±0.8	11.6±1.1	0.294

MPV, mean platelet volume; NLR, Neutrophil to lymphocyte ratio; PNR, Platelet to neutrophil ratio. *Post Hoc analized with tukey test: For platelet: mild versus modarete *P*=0.001 ; mild versus severe *P*=0.059; moderate versus severe *P*=0.979. For lymphocyte: mild versus moderate *P*=0.377; mild versus severe *P*<0.0001; moderate versus severe *P*=0.06. For eosinophil: mild versus moderate *P*=0.985; mild versus severe *P*<0.0001; moderate versus severe *P*<0.0001

Table 3: Comparison of patients according to allergen sensitization

	Patients with sensitization (*n*=71)	Patients without sensitization (*n*=96)	*P*
Platelet (count/mm^3, mean±SD)	449323.9±1.5	417229.1±3.8	0.506
MPV (femtoliter, mean±SD)	8.7±1.1	8.6±1.1	0.82
NLR (ratio, mean±SD)	0.7±0.8	0.9±1.8	0.288
PNR (ratio, mean±SD)	174.1±100.6	183.7±196.8	0.705
Lymphocyte (count/mm^3, mean±SD)	5940.7±2536.1	4708.6±1880.7	< 0.0001
Neutrophil (count/mm^3, mean±SD)	3304.5±2502.7	4036.1±10819.2	0.577
Eosinophil (count/mm^3, mean±SD)	633.5±711.1	397.1±425.4	0.008

MPV, mean platelet volume; NLR, Neutrophil to lymphocyte ratio; PNR, Platelet to neutrophil ratio

that the rate of NLR increases in airway inflammation diseases such as allergic rhinitis, allergic asthma, and bronchiectasis.[20,27,28] In the light of present studies, NLR tends to increase in respiratory allergic diseases, while NLR seems to decrease in cutaneous allergies.

The platelet-lymphocyte ratio (PLR) has been evaluated in many diseases and it was found to be higher in rheumatic diseases and infectious diseases in addition to NLR.[23,24] Because in rheumatic diseases, naive-T lymphocyte differentiates into T helper 17 (Th17) subgroup and activates neutrophils with cytokines.[29] Both NLR and PLR increase as the key immune system cell is neutrophils. However, in the pathogenesis of AD, the naive-T lymphocyte differentiates into the Th2 subgroup and uses cytokines and eosinophils as effector cells. In sum, Th17 and neutrophils and Th2 and eosinophils play a crucial role in rheumatic diseases and allergic diseases, respectively. This is also proven by the fact that the NLR ratio was reversed in our patients with AD. Based on this, we found it appropriate to calculate PNR instead of PLR in our study. We found a significant increase in PNR in patients with AD compared to the control group. We concluded that thrombocytosis and neutrophilia are involved in rheumatic diseases while thrombocytosis, lymphocytosis, and eosinophilia play a role in allergic diseases.

The limitation of our study is that the laboratory results of the patients during the period when they were in remission could not be evaluated due to its retrospective nature. At the same time, there would be a significant contribution if we had performed a lymphocyte subgroup analysis by flow cytometry in patients with AD.

In this study, we found that an increase in TC may be an important laboratory parameter in allergic skin inflammation; however, we demonstrated the dominance of eosinophils and lymphocytes. Finally, we thought that platelets are also involved in allergic skin inflammation such as eczema in correlation with lymphocytes. Because both mean AEC and mean TC were significantly higher in the patient group. There was a positive correlation between both parameters and the SCORAD index.

In conclusion, we found that TC was significantly higher in patients with AD. Similarly, the increase in PNR was remarkable. However, we did not detect a significant difference in MPV values between the patient and control groups. CBC is an easy and inexpensive blood test to study. In the following years, thrombocytosis

and PNR can be evaluated in patients with AD as a biomarker that correlates with the severity of eczema. However, further studies are required for its routine use as an evaluation criterion.

Author contributions

Designed the study: O.A. and I.T. Preparation of ethics forms and apply: O.A. Manuscript preparation and analysis interpretation of data: O.A. and I.T. Contributed reagents/materials/analysis tools: O.A. and I.T. Wrote the paper: O.A. and I.T. Collected and entered the data: O.A. and I.T.

All authors approved the final manuscript as submitted.

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Conflicts of interest

There are no conflicts of interest.

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