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Klinik Araştırma

Inflammatory Markers in Inactive Behçet's Disease

İnaktif Behçet Hastalığı'nda İnflamatuar Belirteçler

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Abstract

Aim: Behçet's disease is a multi-systemic chronic inflammatory disease and many biomarkers and cytokines have been identified in the diagnosis and follow-up of disease activity. Neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) have been used as new inflammatory biomarkers to assess disease severity in many autoimmune diseases. The aim of the study is to investigate the NLR and PLR values of the Behçet patients in the inactive period.

Material and Methods: After the clinical examination and disease activity were evaluated by the internal medicine clinic, the patients who met the inclusion criteria and were considered in inactive period were evaluated in terms of possible inflammatory and malignant diseases by other clinics (otorhinolaryngology, ophthalmology, and dentistry). After exclusion of other causes of increased NLR, 40 Behçet's patients and 45 healthy controls were included in the study. NLR and PLR values of these two groups were compared.

Results: NLR values were statistically higher in the patient group compared to the control group. PLR values were higher in the patient group, but there was no statistical difference

Conclusion: NLR was found to be high even though the patients were in the inactive phase and after other conditions that could cause NLR elevation were evaluated by other clinics. This supports an underlying inflammatory condition in Behçet's disease, even if the patient has no clinical findings and is in the inactive stage.

Keywords: Behçet's disease; neutrophil-to-lymphocyte ratio; platelet-to-lymphocyte ratio; disease activity

Öz

Amaç: Behçet hastalığı kronik multi sistem tulumlu inflamatuar bir hastalıktır ve hastalık aktivitesinin tanı ve takibinde birçok sitokin ve biyobelirteç tanımlanmıştır. Nötrofil-lenfosit oranı (NLR) ve trombosit-lenfosit oranı (PLR), otoimmün hastalıklarda hastalık şiddetini değerlendirmek için yeni inflamatuar biyobelirteçler olarak kullanılmaktadır. Çalışmanın amacı, inaktif dönemdeki Behçet hastalarında NLR ve PLR değerlerini incelemektir.

Gereç ve Yöntemler: Dahiliye kliniği tarafından detaylı sistemik muayenesi yapılan, çalışmaya dahil edilme kriterlerine uyan ve hastalık aktivitesi değerlendirildikten sonra inaktif olarak kabul edilen hastalar çalışmada yer alan diğer kliniklerce (kulak burun boğaz hastalıkları, göz hastalıkları ve diş hekimliği) olası inflamatur ve malign hastalıklar yönünden değerlendirildi. NLR yüksekliği yapabilecek diğer nedenler ekarte edildikten sonra 40 Behçet hastası ve 45 sağlıklı kontrol çalışmaya dahil edildi. Bu iki grubun NLR ve PLR değerleri karşılaştırıldı.

Bulgular: Hasta grubunun NLR değerleri kontrol grubuna oranla istatistiksel olarak daha yüksekti. Hasta grubunda PLR değerleri daha yüksekti ancak istatistiksel olarak anlamlı fark yoktu.

Sonuç: Çalışmadaki hastalarda NLR yüksekliğine neden olabilecek diğer durumlar tüm branşlar tarafından değerlendirildikten sonra ve hastalar inaktif evrede oldukları halde NLR yüksek bulunmuştur. Bu durum Behçet hastalığında hastada klinik bulgu olmasa ve hasta inaktif evrede olsa dahi altta yatan bir inflamatuar durumu desteklemektedir.

Anahtar Sözcükler: Behçet hastalığı; nötrofil-lenfosit oranı; trombosit-lenfosit oranı; hastalık aktivitesi

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Introduction

Behçet's disease (BD) is a chronic multi-systemic inflammatory disease with ocular, mucocutaneous, gastrointestinal, vascular and neurological involvement (1). The diagnosis is based on clinical criteria and there are no pathognomonic laboratory findings (2). Many biomarkers and cytokines have been identified in the diagnosis and monitoring of disease activity. Some of these are antilysozyme, serum endocan, serum growth differentiation factor 15 (GDF-15), serum alpha 1-acid glycoprotein (AGP), interleukin-8 (IL-8), interleukin-32 (IL-32), interferon gamma (IFN-γ), interleukin-20 (IL-20), interleukin-6 (IL-6), tumor necrosis factor-α (TNF- α), interleukin-26 (IL-26) (3-11). However, these are not readily available markers and not routinely utilized in clinical practice.

In recent years, neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) have been identified as new inflammatory biomarkers to assess disease severity in several autoimmune diseases; such as rheumatoid arthritis (RA), ankylosing spondylitis, systemic lupus erythematosus (SLE), and psoriatic arthritis (12-15).

High NLR and PLR levels are indicative of the systemic inflammatory response (16). NLR is used to show the severity of inflammation in autoimmune diseases, diabetes, hypertension and some malignancies (17). PLR is also one of the new biomarkers that indicate inflammation (18). It has been reported that PLR increased in RA and SLE and in hepatocellular carcinoma and gastrointestinal stromal tumors (19-22). There are some studies showing the relationship of NLR and PLR with disease activity in BD (23,24). In our study, unlike other studies, we aimed to examine the NLR and PLR values of the Behçet patients in the inactive period.

Material and method

Ethical approval was obtained from the ethics committee of Adiyaman University Faculty of Medicine (No:2020/6-55). Informed consent obtained from all patients who participated in this study. Patients were selected according to the new international diagnostic criteria of BD (25).

Disease activity was evaluated according to Behçet's Disease Clinical Activity Form (BDCAF) (26). In clinical examination, oral ulcers, genital ulcers, ocular involvement, other skin lesions, joint findings, vascular, neurological, and gastrointestinal involvement were questioned.

Healthy patients defined as those with BDCAF score equal to or higher than two were excluded (27). Fifty-seven patients diagnosed with Behçet's disease were included in our study. Demographic characteristics, height-weight, blood pressure and pulse values of the patients were noted by the internal medicine clinic. Systemic diseases, drug and substance use, smoking, previous operations were questioned and these were excluded from the study. Detailed clinical examinations were performed, and patients with a normal body mass index (BMI) without any disease questioned and these were excluded from the study. Detailed clinical examinations were performed, and patients with a normal body mass index (BMI) without any disease other than Behçet's disease were referred to ear, nose, and throat (ENT), ophthalmology and dentistry clinics. Endoscopic examinations performed in the ENT clinic and detailed clinical examinations in ophthalmology and dentistry were also performed. Forty patients without any signs of infection or malignancy were included in the study.

Forty-five healthy volunteers who did not have a statistically significant difference with the study group in terms of age and gender and who were not diagnosed with any disease after the examinations of internal medicine, ENT, ophthalmology and dentistry were accepted as the control group. The NLR and PLR values of these two groups were compared.

Statistical analysis

The data obtained in this study were analyzed with the SPSS. While investigating the status of variables coming from normal distribution Shapiro Wilk's test was used because of the unit numbers. 0.05 was used as the significance level while interpreting the results; It was stated that if $p < 0.05$, the variables did not come from the normal distribution, and if $p > 0.05$, the variables came from the normal distribution. While examining the differences between groups, Mann Whitney U Test was used because the variables did not come from the normal distribution. While examining the relationships between groups of nominal variables, Chi-Square analysis was applied. 0.05 was used as the significance level while interpreting the results; It was stated that there is a significant relationship when $p < 0.05$, and there is no significant relationship if $p > 0.05$.

Results

According to BDCAF, 43 of the 57 patients were inactive and 40 patients were included in the study after clinical examinations. Eighteen of these patients were female and 22 were male and the average age was 39. There was no statistical difference between the patient and control groups in terms of age and gender (Table 1,2).

Table 1. Gender distribution and comparison between groups

		Behçet Disease		Control		Total			
		n	%	n	%	n	%	Chi Square	P*
Gender	Male	22	55	23	51,1	45	52,9	0,129	0,720
	Female	18	45	22	48,9	40	47,1		
	Total	40	100	45	100	85	100		

*Chi Square Test

Table 2. Age distribution and comparison between groups

		n	Mean	SD	Min	Max	P*
Age	Behçet Disease	40	39,42	10,97	22	66	0,263
	Control	45	36,73	12,27	18	79	
	Total	85	38,0	11,71	18	79	

SD: Standard deviation, Min: Minimum, Max: Maximum, *: Mann Whitney U Test

NLR values were higher in the patient group compared to the control group, and this difference was statistically significant (Table 3). Although PLR values were higher in the patient group, but there was no statistical difference (Table 4).

Table 3. Inverstigation of the relationship between groups in terms of NLR values

		n	Mean	SD	Min	Max	P*
NLR	Behçet Disease	40	2,40	1,45	1	9,13	0,007
	Control	45	1,73	0,55	0,76	3,32	
	Total	85	2,05	1,11	0,76	9,13	

NLR: Neutrophil-to-lymphocyte ratio, SD: Standard deviation, Min: Minimum, Max: Maximum, *: Mann Whitney U Test

Table 4. Inverstigation of the relationship between groups in terms of PLR values

		Group					Mann Whitney U Test
		n	Mean	SD	Min	Max	P*
PLR	Behçet Disease	40	112,77	39,76	40,18	273,15	0,146
	Control	45	101,84	30,47	46,78	206,56	
	Total	85	106,98	35,36	40,18	273,15	

PLR: Platelet-to-lymphocyte ratio, SD: Standard deviation, Min: Minimum, Max: Maximum, *: Mann Whitney U Test

Discussion

Behçet disease is a systemic relapsing inflammatory disease characterized by repeated episodes and neutrophil-predominant inflammation in target tissues (28). In autoimmune diseases, patients' immune systems develop response against self-antigens, and since it is not possible for these self-antigens to completely disappear, there is a constant immune response. Activation of immune pathways and excessive cytokine production result in chronic inflammation causing tissue damage and an increase in inflammatory cells (29).

Leukocytosis and thrombocytosis can be considered as indicators of inflammation in autoimmune diseases such as BD (23). Likewise, NLR and PLR are biomarkers that can be calculated easily, but their clinical use is still unclear. There are studies in the literature indicating that NLR and PLR are increased in BD (24,30,31).

Geita et al. found both NLR and PLR higher in BD compared to healthy controls (31). In their study on 254 patients with BD, Alan et al. found NLR and PLR significantly higher but stated that there was no correlation with the severity of the disease (29). Balta et al. compared NLR in healthy and inactive Behçet patients and found it significantly higher values in healthy patients (23). Hammad et al. compared 16 healthy patients with 17 inactive patients and they found a statistically significant difference and stated that the NLR and PLR correlated with BDCAF (30).

Vaya et al. found that red blood cell distribution width (RDW) was higher in inactive Behçet's patients than healthy controls, but there was no correlation between RDW and inflammatory markers (32).

Uluyol et al. examined mean platelet volume (MPV) and NLR values in healthy and inactive periods of patients with recurrent aphthous stomatitis (RAS) and found significantly higher values in healthy patients (33). They argued that these values could be used to predict RAS activation.

The most important difference in our study is that all the patients were in the inactive period and these patients were examined by otolaryngologists, ophthalmologists and dentists in terms of both BD and other infectious and malignant causes with a multidisciplinary approach.

Since we believe that the retrospective data and the information obtained by calling the patients by phone are not reliable, and the patients may not accept the some symptoms as disease activation by taking them for granted, or they may ignore the inflammatory conditions such as common cold, periodontitis and conjunctivitis by not accepting serious infection when asked.

There are studies in the literature that argue NLR is more significant than PLR as an indicator of inflammation (30,34).

As a result, we found that NLR was significantly increased in inactive BD patients compared to healthy controls, but there was no statistical significance in PLR.

The fact that NLR is significantly higher even in the inactive state may indicate that there is no complete remission in BD, and that there is an autoimmune response in standby state that can be activated at any time or NLR may be an overrated laboratory finding that is not correlated with the clinical course of disease.

As a limitation of our study, even if the patients were systematically examined in detail by the internal medicine, some gynecological and urological diseases may have been overlooked. For this reason, when evaluating laboratory parameters in Behçet's disease that progress with activation and remission periods, all other conditions that can change these parameters should be taken into consideration and patients should not be hesitated to consult other clinics.

Conclusion

We found that NLR was significantly increased in

inactive BD patients compared to healthy controls, but there was no statistical significance in PLR. More comprehensive studies are needed, especially involving inactive BD patients, and indeed excluding other inflammatory conditions. Laboratory studies are meaningful when evaluated with the clinical condition of the patients. And before the studies with inflammatory markers, patients should be examined in detail by many medical specialties in terms of possible inflammatory and malignant diseases.

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OYA: Study design, examination of patients, data collection and analysis, manuscript development, review of final manuscript, AK: Study design, examination of patients, data collection and analysis, manuscript development, review of final manuscript, ASK: Study design, examination of patients, data collection and analysis, manuscript development, review of final manuscript, AA: Study design, data collection and analysis, manuscript development, review of final manuscript, DIB: Study design, examination of patients, data collection and analysis, manuscript development, review of final manuscript, IC: Study design, data analysis, manuscript development, review of final manuscript.

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