Neutrophil/Lymphocyte Ratio, Platelet/Lymphocyte Ratio and Mean Platelet Volume in Behçet Disease Patients with and without Ocular Involvement

Göz Tutulumu Olan ve Olmayan Behçet Hastalarında Nötrofil/Lenfosit Oranı, Trombosit/Lenfosit Oranı ve Ortalama Trombosit Hacmi

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ABSTRACT Objective: To evaluate the relationship between neutrophil/lymphocyte ratio (NLR), mean platelet volume (MPV), and platelet/lymphocyte ratio (PLR) and risk of ocular involvement in Behçet Disease (BD). **Material and Methods**: This prospective randomised study included 45 patients with ocular BD (Group1), and 86 patients with BD without ocular involvement (Group2) and 90 control subjects. The NLR, MPV, PLR and other laboratory tests were evaluated in the groups. **Results:** A significant difference was found in NLR and PLR values between patients with BD (n=131) and control subjects (n=90) (p<0.001). No statistically significant difference in laboratory parameters was found in BD group without ocular involvement when compared with ocular BD group, except MPV level. There was a positive correlation between MPV and activation of ocular BD (p<0.001). In the receiver-operating characteristic analysis, MPV cut off point was 8.80 and predicted the presence of active ocular BD with 66.7% sensitivity and 60.4% specificity. HLA-B51 positivity is higher in patients with ocular BD than BD without ocular involvement (p<0.001). **Conclusion:** Our results show that increased NLR and PLR levels may predict BD. Although NLR, and PLR are higher in BD patients, no differences were found when comparing patients with and without ocular involvement. The MPV may be a simple, inexpensive, and convenient diagnostic marker of active ocular BD.

Key Words: Platelet activation; Behcet syndrome; neutrophil activation

ÖZET Amaç: Behçet hastalığında oküler tutulum riski ile nötrofil / lenfosit oranı (NLO), trombosit/lenfosit oranı (PLO) ve ortalama trombosit hacmi (OTH) arasındaki ilişkiyi değerlendirmek. **Gereç ve Yöntemler:** Bu prospektif randomize çalışmaya 45 oküler tutulumu olan Behçet hastası (Grup 1) ile 86 göz tutulumu olmayan Behçet hastası (Grup 2) ve 90 kontrol olgusu dahil edildi. Üç grupta NLO, OTH, PLO ve diğer laboratuar testleri değerlendirildi. **Bulgular:** Behçet hastaları (n=131) ile kontrol grubu (n=90) arasında NLO ve PLO değerleri arasında anlamlı fark bulundu (p <0,001). OTH düzeyi haricinde oküler Behçet hastalığı grubuyla göz tutulumu olmayan Behçet hastalığı grubu arasında laboratuvar parametrelerinde istatistiksel olarak anlamlı fark izlenmedi. Aktif oküler Behçet ile OTH arasında pozitif korelasyon saptandı (p <0,001). ROC eğrisinde, MPV eşik değeri 8,80 idi ve %66,7 duyarlılık ve %60,4 spesifite ile aktif oküler Behçet hastalığı varlığını gösterdi. Göz tutulumu olan Behçet hastalığında göz tutulumu olmayanlara göre HLA-B51 pozitifliği daha yüksekti (p<0,001). **Sonuçlar:** Sonuç olarak laboratuvar parametrelerine bakacak olursak NLO ve PLO değerleri Behçet hastalığında aktivasyon göstergesidir. Ancak oküler tutulumu olan ve olmayan Behçet hastalarında NLO ve PLO düzeyleri arasında bir fark izlenmedi. OTH, Behçet hastalarında aktif oküler tutulum için basit, ucuz ve kullanışlı tanısal belirteç olabilir.

Anahtar Kelimeler: Trombosit aktivasyonu; Behçet sendromu; nötrofil aktivasyonu

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Behçet's disease (BD) is a chronic multisystemic inflammatory disorder characterized by immune-mediated occlusive vasculitis. It involves mucocutenous, ocular, articular, neurological, and vascular manifestations. The typical form of ocular involvement is relapsing-remit-

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ting uveitis. It may present as iridocyclitis with hypopyon, vitreitis and retinitis, panuveitis, occlusive vasculitis and cystoid macular edema.[1-3]

The pathophysiology of ocular BD is not clearly known. Several mechanisms such as genetics, infection, immune complexes and antibodies have been suggested as causes of this disease. The vascular inflammatory change is known to be the main histopathology.[4,5] There is no sensitive or spesific laboratory test or pathologic findings. But in the previous studies, it was reported that the increased blood levels of acute phase proteins, erythrocyte sedimentation rate, rheumatoid factor, C-reactive protein, neopterin, a1-antitrypsin, a2-macroglobulin were correlated with disease activity.[6] Some markers including interleukin (IL), IL-1b, tumor necrosis factor a (TNF-a), thrombomodulin, E-selectin, vascular endothelial growth factor, and homocysteine had been considered as inflammatory indicators in BD.[6] And the affected organs show neutrophil and lymphocyte infiltration.[7,8]

In recent years, the neutrophil/lymphocyte ratio (NLR), mean platelet volume (MPV), and platelet/lymphocyte ratio (PLR) has been shown as potential markers of inflammation in vascular disorders. There are several studies assessing NLR, PLR and MPV in various diseases including BD, keratoconus, age related macular degeneration, nonarteritic ischemic optic neuropathy, psoriasis, familial mediterranean fever, cardiovascular diseases and malignancies.[9-19] An association between NLR, MPV levels and BD has been investigated previously.[5,7,17] According to our literature research, there is no current study examining the value of these markers's levels in the diagnosis of ocular BD.

In this study, we aimed to evaluate the relationship between NLR, MPV, PLR and other laboratory tests and risk of ocular involvement in BD.

MATERIAL AND METHODS

The study was conducted prospectively in the Consultation Service of the Ophthalmology Department, Akdeniz University between May 2013 and February 2015, and approved by the local ethics committee. Written informed consent was obtained from each subject after they were provided with an explanation of the nature of the study. The study included 45 patients with active ocular BD (Group 1), and 86 patients with BD without ocular involvement (Group 2). The study included age-sex matched 90 healthy subjects in the control group (Group 3). The diagnosis of BD was based on the criteria of the International Study Group for Behçet's Disease.[20] Also, all patients were evaluated in Rheumatology and Dermatology clinics. Patients with any systemic such as diabetes mellitus, hypertension, autoimmun diseases, cancer and other ocular diseases such as ocular infection, retinopathy, glaucoma, vascular diseases, optic neuropathy were excluded from the study. Patients with the history of hormone replacement therapy, antiplatelet therapy, antioxidant therapies, and immunosuppressive therapy were also excluded.

All participants received a complete ocular examination including best-corrected visual acuity on a Snellen scale, slitlamp biomicroscopy, intraocular pressures (IOP) measurement with Goldmann applanation tonometry, and indirect ophthalmoscopy. Slit-lamp biomicroscopy was performed to detect inflammation. The presence of vasculitis, retinitis, papillitis, and CME was confirmed by fluorescein angiography (FFA) and optical coherence tomography (OCT). The anatomic location of inflammation included anterior uveitis, posterior uveitis, or panuveitis according to the Standardized Uveitis Nomenclature classification system was noted in all patients.[21] Patients who experienced only attacks of iridocyclitis were classified as having anterior uveitis; patients who experienced retinitis, retinal vasculitis, and/or papillitis without significant iridocyclitis were classified as posterior uveitis; and patients who had both significant anterior and posterior uveitis were defined as panuveitis. Inflammatory status had been categorized by the same physician for every eye at the time of each visit. The study defined "slightly active" inflammation when described as mild or a few cells. Inflammation was scored as inactive when described by terms such as quiet or no cells.

Patients's data were reviewed in order to investigate the clinical characteristics of BD, and laboratory tests results. Laboratory tests included NLR (absolute neutrophil-to-absolute lymphocyte ratio), MPV, PLR, and HLA-B51 genotype. Total WBC count, neutrophil, and lymphocyte differentials were determined using an automated blood cell counter (Siemens Advia 2120 Analyzer). Complete blood counts were measured by the method of laser-based flow cytometric impedance (BN2 Siemens). The NLR and PLR were calculated by dividing the neutrophil and platelet count by lymphocyte count. These parameters are tested as risk markers for ocular involvement in Behçet patients.

The data was evaluated using SPSS (Statistical Package for Social Sciences) 20.0 program for Windows. Categorical variables were compared with the chi-square test. Categorical variables were given as the number of cases and percentages. Kolmogorov-Smirnov test was used to test for normality of the data. Continuous data were given as mean±SD. Data with a normal distribution were compared by Student's t test. Comparisons of continuous variables with an asymmetric distribution were made by using the Mann-Whitney U test. Multivariate analysis was performed using a logistic regression model to evaluate the ocular involvement associated with MPV values. Receiver-operating characteristic (ROC) analyses was used to compare the performance and prognostic power of the MPV. The predictive validities were quantified as the area under the ROC curves (c statistics), and the comparisons of c statistics were performed by MedCalc statistic software (version 11.3.8.0, Mariakerke, Belgium). A p value less than 0.05 was considered statistically significant.

RESULTS

(Table 1) shows the demographic and laboratory characteristics of the control subjects and patients with BD. The counts of white blood cell, neutrophil, and platelet, and NLR, PLR levels were higher in patients with BD than control group. MPV level was not statistically different between the two groups (p=0.305).

TABLO 1: The demographic and laboratory characteristics of the patients with Behçet Disease and control groups.

	Group 1 (n=131)	Group 2 (n=90)	P value
Age (year)	42,7±12,4	41,9±11,1	0,089
Male/Female	74/57	52/38	0,81
WBC	8,41±1,52	7,18±1,42	<0,001
Neutrophil (10^3/ml)	5,64±1,96	3,57±1,19	< 0,001
Lymphocyte (10^3/ml)	2,12±0,54	2,08±0,76	0,12
Platelet (10^3/ml)	286,96±73,4	254,64±85,9	< 0,001
NLR	3,26±2,78	1,84±1,29	< 0,001
PLR	165,18±44,4	119,46±57,0	< 0,001
MPV	8,95±1,81	7,65±1,92	0,30

WBC:White blood cell, NLR: Neutrophil/lymphocyte ratio, PLR: Platelet/lymphocyte ratio, MPV: Mean platelet volume.

(Table 2) shows the demographic and clinical characteristics of the patients in the Group 1 and 2. The age, gender distributions and the mean duration of disease were similar in both main groups. Panuveitis was frequently observed as ocular involvement in Group 1 (p<0.001). And also, there were retinal vasculitis in 24 patients that was

TABLO 2: The demographic and clinical characteristics of the patients.

	Group 1 (n=45)	Group 2 (n=86)	P value
Male/Female	28/17	46/40	0,19
Mean age (year)	43,4±10,7	41,9±9,6	0,09
Mean duration of disease (month)	68,3±45,7	74,7±52,6	0,21
Ocular involvement			
Anterior uveit	2	-	
Posterior uveit	17	-	
Panuveit	26	-	
HLA-B51	27 (60%)	38 (44,1%)	<0,001
Pathergy test	14 (31,1%)	36 (41,8%)	0,08
Oral ulcer	-	48 (55,8%)	
Genital ulcer	-	39 (45,3%)	
Erythema nodosum	-	34 (39,5%)	
Papulopustular lesion	-	40 (46,5%)	
Arthritis	-	28 (32,5%)	
Neuro-Behçet	-	5 (5,86%)	
GIS manifestation	-	3 (3,48%)	
Thrombophlebitis	-	7 (8,13%)	

GIS: Gastrointestinal system.

shown in the FFA. HLA-B51 positivity is higher in patients with ocular BD than BD without ocular involvement (p<0.001).

The laboratory findings of the patients in Group 1 and 2 were summarized in Table 3. However, no statistically significant difference in laboratory parameters was found in BD group when compared with ocular BD group, except MPV level. A multivariate logistic regression model was used to determine whether there was a significant difference in uveitis according to laboratory findings. We found that only MPV level was associated with ocular involvement with an OR of 4.14 (95% CI, 1.01-3.22; p =0.041). Graph 1 shows the MPV values in the ROC analysis to distinguish BD with or without ocular involvement, the area under the curve value of the MPV was found to be 0.641 (with a standard error of 0.038 and P <0.001). The best cut off point was 8.80 with a sensitivity of 66.7% and a specificity of 60.4% (Figure1).

DISCUSSION

In this study, we investigated NLR, MPV, PLR and other laboratory tests in Behçet patients with and without ocular involvement. We wondered whether NLR, MPV and PLR can be used as an indicator for ocular BD risk in Behçet patients. Our findings indicated that increased NLR and PLR levels may predict BD. Our results show that although NLR, and PLR are higher in BD patients, no differences were found when comparing patients with and without ocular involvement. In the ocular BD group, the MPV and HLAB51 positivity were found to be significantly higher than BD without ocular involvement group.

TABLO 3: The demographic and laboratory characteristics of the patients with Behçet Disease and control groups.

	Group 1 (n= 45)	Group 2 (n=90)	P value
WBC	8,72±1,94	8,36±1,79	0,05
Neutrophil (10^3/ml)	5,54±1,76	5,27±1,78	0,07
Lymphocyte (10^3/ml)	2,01±0,98	2,09±0,53	0,37
Platelet (10^3/ml)	28,3±78,2	28,7±68,0	0,73
NLR	3,96±3,52	3,69±1,59	0,15
PLR	165,4±74,6	149,4±67,65	0,25
MPV	10,07±0,56	8,42±0,98	<0,001

WBC:White blood cell, NLR: Neutrophil/lymphocyte ratio, PLR: Platelet/lymphocyte ratio, MPV: Mean platelet volume.

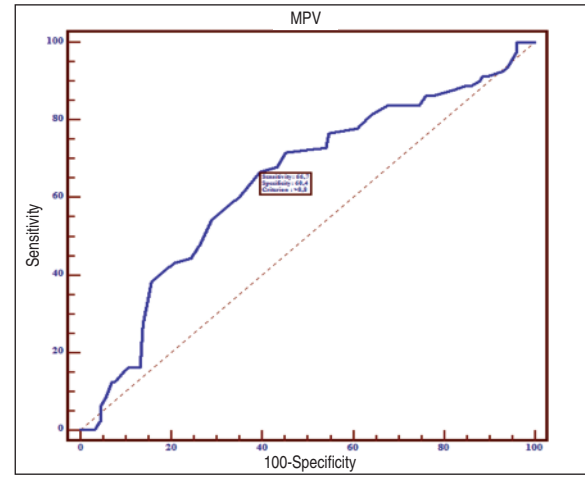

FIGURE 1: Receiver-operating characteristic curve of the mean platelet volume for predicting ocular Behçet Disease.

The exact mechanisms underlying the pathogenesis and the prognosis of ocular BD still remain unknown. The major histopathological features is vasculitis with neutrophil and monocyte infiltration in the perivascular region and autoimmune response.[22] Many inflammatory mediators were shown in relation to BD. High serum levels of interleukin IL-2 and pro-inflammatory cytokines IL-1b, IL-6, TNF-alpha and IL-8, had been considered as active inflammatory markers, indicate a polarized T helper 1 immune response. TNF-alpha and IL-8 are potent chemoattractant for neutrophils, and promotes the expression of adhesion molecules on endothelial cells, helping neutrophils migration. Increased IL-6 levels are responsible for inducing platelet production by inducing the size of platelets by influencing megakaryopoiesis and releasing big sized platelets from the bone marrow. But these activation biomarkers are expensive and not use routinely.[5,22-24] Previous studies showed that blood parameters like neutrophils, platelet activities are increased in BD.[5,22] Recently, NLR, MPV and PLR has been proposed as a simple and reliable indicator for systemic inflammation in several diseases.[9-17] They are also simple to calculate, readily available, and cost effective.

Most recent studies have assessed NLR as an index of systemic inflammatory conditions that correlate with prognosis and severity of diseases.[25,26] The MPV and PLR are also accepted as a sign of inflammation.[12-14,27] Platelets secrete proinflammatory substances such as chemokines and cytokines that mediate vascular inflammation. Platelet markers such as P-selectin, CD40 and CD62 ligand, matrix metalloproteinase, beta-thromboglobulin, PF-4 and platelet leukocyte aggregates have a role in the spread of inflammation and platelet aggregation in inflammatory diseases.[9] MPV and PLR are also predicted the platelet activation.[5,12-14,27-29]

Öztürk et al. investigated the correlation between NLR and inflammatory activity in BD.[7] They observed that NLR levels were significantly higher in active patients with BD than in inactive patients. And they noticed that NLR is a simple method that will allow us to show the activity of BD. In our study, patients with or without ocular BD had significantly higher NLR, MPV and PLR levels compared with controls, as an indicator of inflammation. But we did not find any differences in NLR and PLR when comparing patients with and without ocular involvement, except MPV. The MPV result of 8.80 predicted the presence of ocular involvement with 66.7% sensitivity and 60.4% specificity.

In the ophthalmology literature, Ricart et al. investigated whether MPV is involved in the pathogenesis of thrombotic events and posterior uveitis.[30] They did not observe any effect of the presence of posterior uveitis or thrombosis on MPV levels in BD. But the posterior uveitis group in their study were not in the active phase and most of them had received immunosuppressant therapy. Türkçü et al's study included only ocular BD patients with active panuveitis attack without initial medications that might impair MPV measurements.[31] They observed that there was a significant difference between the initial measurements of the ocular BD. But they suggested that MPV is not a predictive laboratory test to determine the clinical improvement in early stages following classical immunosuppressive treatment in ocular BD.

In our study, HLA-B51 was found to be frequent in patients with ocular BD. Previous studies suggest that the HLA-B51 gene might play a role in the persistent progression for neuro-Behçet development in BD.[32,33] According to literature search in PUBMED, there are no studies correlating HA-B51 and ocular BD.

The major limitation of this study is a statistical analysis was not done for the correlation between MPV value and anatomical localization of uveitis. For all that, our study has a prospective nature and our sample sizes in the two groups were enough for a reliable statistical analysis. And to the best of our knowledge, this is the first study to investigate NLR and PLR in patients with ocular BD.

In conclusion, our results support the relationship between the BD and increased systemic inflammatory response (NLR, PLR). And the MPV may be a simple, inexpensive, and convenient diagnostic marker of active ocular BD. However, for proposing MPV as a systemic inflammation in patients with ocular BD, further randomized prospective studies with a larger sample size are required.

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