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Comparison of the hematological parameters of recurrent aphthous stomatitis and Behçet's disease

Tekrarlayan aftöz stomatit ile Behçet hastalığında hematolojik parametrelerin karşılaştırılması

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Abstract

Background and Design: Hematological parameters have been used as laboratory markers to evaluate the systemic inflammation in several rheumatic disease. The aim of this study is to determine the difference of hematological parameters between the patients who have been just fulfilled the Behçet's disease (BD) criteria and patients with recurrent aphthous stomatitis (RAS).
Materials and Methods: Twenty patients with newly diagnosed BD and 47 patients with RAS whose oral ulcerations appeared at least three times a year were enrolled in this cross-sectional study. Demographic and clinical characteristics of patients, complete blood count, C-reactive protein (CRP) and erythrocyte sedimentation rate were recorded.
Results: Patients' characteristics including gender, age, duration, and frequency of oral aphthous ulcerations in both study groups were comparable (p>0.05). CRP was significantly higher in newly diagnosed BD group when compared to the RAS group (p=0.001). CRP value higher than 2.7 g/dL, mean platelet volume (MPV) value higher than 7.58 fL and lymphocyte count higher than 2.85 10^3/μL were found to be the markers for distinguishing patients with BD from patients with RAS [odds ratio (OR): 12.76 (95% confidence interval (CI): 2.86-56.88), OR: 5.61 (95% CI: 1.11-28.42), OR: 15.24 (95% CI: 1.77-131.31), respectively].
Conclusion: The elevated CRP, MPV and lymphocyte count were associated with patients with newly diagnosed BD rather than patients with RAS. Further large prospective studies with the healthy control group are needed to confirm these findings.
Keywords: Behçet disease, recurrent aphthous stomatitis, blood cell count

Öz

Amaç: Hematolojik parametreler çeşitli romatizmal hastalıklarda sistemik enflamasyonu değerlendirmek için laboratuvar belirteçleri olarak kullanılmaktadır. Bu çalışmanın amacı; Behçet hastalığı (BH) kriterlerini yeni karşılayan hastalar ile rekürren aftöz stomatit (RAS) tanısı alan hastalar arasındaki hematolojik parametrelerin farkını belirlemektir.
Gereç ve Yöntem: Bu kesitsel çalışmaya yılda en az üç kez oral ülserasyonları ortaya çıkan yeni tanı almış 20 Behçet hastası ve 47 RAS tanılı hasta dahil edildi. Hastaların demografik ve klinik özellikleri, tam kan sayımı, C-reaktif protein (CRP) ve eritrosit sedimentasyon hızı kaydedildi.
Bulgular: Her iki çalışma grubunda da hastaların cinsiyet, yaş, oral aftöz ülserasyon süresi ve sıklığı gibi özellikleri benzerdi (p>0,05). CRP, yeni tanı alan BH grubunda RAS grubuna göre anlamlı düzeyde yüksekti (p=0,001). CRP değerinin 2,7 g/dL'den yüksek, ortalama trombosit hacmi (MCV) değerinin 7,58 fL'den yüksek ve lenfosit sayısının 2,85 10^3/μL'den yüksek olmasının Behçet hastalarını RAS hastalarından ayırmada belirteç olarak belirlendi [sırasıyla; olasılık oranı (OO): 12,76 (%95 güven aralığı (GA): 2,86-56,88), OO: 5,61 (%95 GA: 1,11-28,42), OO: 15,24 (%95 GA: 1,77-131,31)].
Sonuç: Yüksek CRP, MCV ve lenfosit sayısı, RAS hastalarından ziyade yeni tanı almış Behçet hastaları ile ilişkiliydi. Bu bulguların doğrulanması için sağlıklı kontrol grubuyla daha geniş hasta sayılarını içeren prospektif çalışmalara ihtiyaç vardır.
Anahtar Kelimeler: Behçet hastalığı, rekürren aftöz stomatit, kan hücresi sayımı

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Introduction

Recurrent aphthous stomatitis (RAS) is the most common disease of the oral mucosa with a prevalence of 5-25%. The peak occurrence of RAS is between 10 and 29 years of age. Its etiopathogenesis is not well understood, although several triggering factors including genetic predisposition, viral and bacterial infections, nutritional deficiencies, stress, systemic diseases, and hormonal level fluctuations, have been suggested[1]. It can manifest as simple aphthosis with milder severity or complex aphthosis, which is more severe and may be associated with the conditions mentioned above, including Behçet's disease (BD)[2].

BD is a chronic relapsing multisystemic disease characterized by recurrent oral and genital aphthous ulcerations, skin lesions, ocular, gastrointestinal, neurologic, and articular manifestations. It was first described by Dr. Hulusi Behçet, a famous Turkish dermatologist, in 1937[3]. Among the regions on the Antique Silk Road, BD is most common in Türkiye with a prevalence of 20-420/100,000[4]. RAS is the initial sign of BD in most of the patients[3]. In a prospective study of 67 patients with only complaint of RAS, one of the other diagnostic findings of BD appeared in 52.2% of patients at an average of 7.7 years after the onset of oral ulceration[5]. Although primary aphthous ulcerations and involvement of multiple mucosal areas are more common in the BD than in RAS, it is generally difficult to distinguish these two similar conditions clinically[6-8].

Significant differences in the frequency of HLA-23, HLA-B13 and HLA-DR10 were determined between the Turkish patients with BD and RAS, indicating that these disorders are not in the same spectrum[9]. Detection of a Th2 cytokine, interleukin 4, within the oral lesions of BD patients but not in RAS patients and more sensitive pathergy test results with self-saliva in BD patients were the other differences determined in these patient groups[10,11].

Recently, hematological parameters that are cheap, non-invasive, and easy to perform, have been used as laboratory markers to evaluate systemic inflammation in several rheumatic diseases[12]. To the best of our knowledge, there are only three studies investigating these laboratory markers to distinguish BD from RAS, none of which have compared them between newly diagnosed BD patients and RAS patients. In this study, we aimed to determine the difference of the hematological parameters between these two patient groups.

Materials and Methods

A cross-sectional study was performed in Bilecik State Hospital between December 2013 and January 2020 to evaluate patients with recurrent oral ulcerations. Clinical data were assessed after the approval of the Bilecik State Hospital Local Ethics Committee (approval number: 2020/001, date: 05.02.2020). Informed consent was obtained. Forty-seven patients with RAS and 20 patients with newly diagnosed BD, whose oral ulcerations appeared at least three times a year and who were 18 years old or older, were enrolled in our study. All patients with BD had recurrent oral ulcerations as the initial disease finding, and the diagnosis of BD was based on the International Study Group for BD (which requires the occurrence of at least three episodes of oral ulceration within a 12-month period plus two of the following features: genital ulceration/scar, skin lesions, eye involvement or pathergy test positivity)[13]. The severity score of the BD was determined using the Krause activity index. The severity score is calculated as the sum of 1 point for each mild symptom, 2 points for each moderate and 3 points for severe disease findings based on the study by Krause et al.[7] According to the total score, patients were divided into three groups as mild (<4), moderate (4-6) and severe (≥7) disease.

Patients with RAS were also evaluated according to the criteria of the International Study Group for BD, including medical history, skin examination, pathergy test, and ophthalmological examination. Patients with the following conditions were excluded from the study in both study groups, such as previous BD diagnosis, incomplete BD, other inflammatory diseases, malignancies, immunosuppressive or colchicum treatment, and active infections. The patients' ages, duration and frequency of oral ulcerations, presence of oral and genital ulcerations, skin manifestations of BD (erythema nodosum, papulopustular lesions), ocular involvement, pathergy test results and other manifestations of the disease were recorded. Complete blood count, C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) were obtained for both study groups at the initial diagnosis. The complete blood count was measured with Cell Dyn 3700 with the capabilities of laser and impedance methods. Beckman Coulter AU2700 with the capability of turbimetric assay was used for CRP, and Alaris ALS-100 determined ESR with the Westergren method. The neutrophil, lymphocyte, monocyte, and platelet count, and the levels of hemoglobin, mean platelet volume (MPV), mean corpuscular volume (MCV) and red cell distribution width (RDW) were recorded. The neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR) and monocyte-to-lymphocyte ratio (MLR) were calculated from these parameters.

Statistical Analysis

All statistical analyses were performed with Statistical Package for Social Sciences for Windows 22.0. Descriptive data were given as mean, median, standard deviation and percentage values. The Shapiro-Wilk test was used to test normality of the study groups. Differences in the continuous variables between the study groups were evaluated with the Student's t-test or Mann-Whitney U test. The Spearman's rank correlation coefficient was used to assess the relationship between the continuous variables. The chi-square test was used for nominal variables, and the Mann-Whitney U test was used for the ordinal variables. The receiver operating characteristic (ROC) analysis was performed on continuous variables. The most appropriate cut-off value was determined according to the Youden index, and based on these values, dichotomous variables were created. Categorical variables were given as frequencies and percentages, and "Fisher's exact test" method was used to compare their distributions. The association of hematologic parameters with BD and RAS groups was determined using univariate analysis and a multivariate logistic regression model with a backward stepwise (Wald) method. All tests were two-tailed and were considered statistically significant for p-values below 0.05.

Results

A total of 67 patients with oral aphthous ulcers that recurred at least three times a year were enrolled in this study. The mean age of the BD group and RAS group were 31.65±7.6 and 35.26±14.4, respectively. Patients' characteristics, including gender, age, duration, and frequency

of oral aphthous ulcerations in both study groups, were comparable (p>0.05) (Table 1).

Genital ulcerations (n=16; 80%) and papulopustular lesions (n=14; 70%) were the most common findings accompanying oral aphthous ulcerations, followed by pathergy positivity in 12 patients (60%) and erythema nodosum in four patients (20%). Five patients (25%) had ophthalmic involvement, and one patient (5%) had superficial thrombophlebitis. The mean disease severity score was 3.15±0.74.

Comparisons of hematological parameters between newly diagnosed BD and RAS groups are shown in Table 2. CRP was significantly elevated in the newly diagnosed BD group compared to the RAS group (p=0.001). Other hematological parameters, including hemoglobin, MCV, RDW, MPV, NLR, MLR, PLR, ESR and platelet, neutrophil, lymphocyte, and monocyte values did not differ between the two groups (Table 2). ROC was carried out to calculate the cut-off value of the hematological parameters in distinguishing patients with BD and RAS. The cut-off value of these parameters and their comparison between the study groups are given in Table 2. The distribution of the frequencies of MPV, lymphocyte count, CRP and ESR according to cut-off values (7.58, 2.85, 2.7, 13, respectively) were statistically different between BD and RAS groups (p=0.026, p=0.007, p=0.001, p=0.026 respectively). After determining the cut-off values, hematological parameters were analyzed as dichotomous variables to evaluate the odds ratios using univariate analysis and a multivariate logistic regression model with a backward stepwise (Wald) method. Using youden index for optimal cut-off point, CRP value higher than 2.7 g/dL, MPV value higher than 7.58 fL and lymphocyte count higher than 2.85 $10^3/\mu L$ were found to be the markers for distinguishing patients with BD from patients with RAS [odds ratio (OR): 12.76 (95% confidence interval (CI): 2.86-56.88], OR: 5.61 (95% CI: 1.11-28.42), OR: 15.24 (95% CI: 1.77-131.31), respectively] (Table 3).

Moderate to good correlation was determined between CRP and NLR, while mild-to-moderate correlation was observed between CRP and ESR in the BD group (p=0.019*, p=0.026*, respectively). There was no correlation between CRP and the other hematological parameters in the BD group. There was also a positive correlation between CRP and MLR in the RAS group (p=0.012).

Discussion

BD is a chronic relapsing autoinflammatory disease with neutrophilic inflammation in which oral aphthous ulceration is the initial symptom in most of the patients. Due to the absence of any specific laboratory tests for predicting the development of BD, it is essential to follow-up patients with recurrent oral ulcerations regarding the appearance of other signs of BD[3].

Hematological parameters and blood cell ratios, including PLR, NLR and MLR, have been widely evaluated to diagnose and assess the activity of various inflammatory rheumatic diseases, including BD[12]. Although statistical differences of these inflammatory markers between BD and healthy controls have been well studied, only three studies evaluate the difference in the hematological parameters between BD and RAS. Besides, some of the results in these studies are contradictory, and none of the studies evaluated the newly diagnosed BD patients, so the difference in the hematological parameters between the patients with BD and RAS is yet to be determined.

The shifts in blood cell ratios are affected by several factors, the most important of which is medical history[13]. Djaballah-Ider and Touil-Boukoffa[14]. revealed that NLR was significantly decreased in patients with active BD under combined colchicine-corticosteroid treatment compared to those without treatment. Furthermore, significant decreases in NLR, white blood cell count and RDW were detected after three months of colchicine treatment in RAS patients[15]. Therefore, in our study, to eliminate the possible effects of the medical treatments on the blood cell ratios, the comparison was made between the RAS patients and BD patients who had met the BD criteria and did not use any medications, including immunosuppressive drugs and/or colchicine treatment before.

Because neutrophil hyperactivity is the most important factor in BD pathogenesis, NLR has been widely used to evaluate the activity and

Table 1. Patient characteristics

Characteristics	Total, (n=67)	Behçet's disease, (n=20)	Recurrent oral aphthosis, (n=47)	p
Gender, n (%)				
Male	35 (52.2%)	14 (70%)	21 (44.7%)	0.067
Female	32 (47.8%)	6 (30%)	26 (55.3%)	
Age; mean ± SD (min.-max.)	32±12.8 (18-67)	31.65±7.6 (18-52)	35.26±14.4 (18-67)	0.701 0.048*
≤37	44 (65.7%)	17 (85%)	27 (57.4%)	
>37	23 (34.3%)	3 (15%)	20 (42.6%)	
Duration of oral aphthosis (years) Mean ± SD (min.-max.)	4.8±4.6 (1-20)	4.43±2.94 (1-11)	6.10±5.29 (1-20)	0.473
Frequency of oral aphthosis, n (patient count)	Continuously repetitive: 5 Four times/month: 8 Three times/month: 2 Twice/month: 5 Once/month:18 Once/2 months: 3 Once/3 months: 1 Once/4 months: 25	Continuously repetitive: 1 Four times/month: 4 Three times/month: 1 Twice/month: 1 Once/month: 6 Once/2 months: 2 Once/4 months: 5	Continuously repetitive: 4 Four times/month: 4 Three times/month: 1 Twice/month: 4 Once/month: 12 Once/2 months: 1 Once/3 months: 1 Once/4 months: 20	0.289

*Comparison of the distributions according to cut-off value. SD: Standard deviation, min.: Minimum, max.: Maximum

severity of the disease and its association with the different organ system involvements in BD[16,17]. High NLR corresponds to neutrophilia or lymphopenia, whereas low NLR corresponds to lymphocytosis or neutropenia[18]. In a recent meta-analysis encompassing 14 studies, NLR was significantly increased in the BD group than in the healthy control group [standardized mean difference (SMD), 1.176; 95% CI, 0.392-1.960, p=0.003]. Additionally, it was shown that NLR was higher in the active BD group than in the inactive BD group (SMD, 1.774; 95% CI, 0.179-3.368, p=0.029), while it did not differ between the BD group with thrombosis and those without thrombosis[19]. In a subsequent study evaluating the diagnostic value of the combination of NLR and hemoglobin, NLR was found to be significantly higher, while

Table 2. Hematological parameters of patients with Behçet's disease and recurrent aphthous stomatitis

Hematological parameters median (range)	Total (n=67)	BD patients	RAS patients	p[a,b]
Hemoglobin (g/dL)	13.6 (9.7-17)	14 (11.6-17)	13.8 (9.7-17)	0.762
≤14.9	48 (71.6%)	16 (80%)	32 (68.1%)	0.387
>14.9	19 (28.4%)	4 (20%)	15 (31.9%)	
MCV (fL)	87.6 (49.1-98)	87.2 (49.1-91.4)	87.7 (70-98)	0.307
≤88.5	43 (64.2%)	15 (75%)	28 (59.6%)	0.275
>88.5	24 (35.8%)	5 (25%)	19 (40.4%)	
RDW (%)	15.4 (12.3-37.1)	15.2 (12.5-37.1)	15.4 (12.3-21.6)	0.602
≤14.3	16 (23.9%)	8 (40%)	8 (17%)	0.062
>14.3	51 (76.1%)	12 (60%)	39 (83%)	
Platelet (10^3/mL)	247.0 (146-455)	263.5 (183-365)	246 (146-455)	0.197
>253	31 (46.3%)	11 (55%)	20 (42.6%)	0.426
≤253	36 (53.7%)	9 (45%)	27 (57.4%)	
MPV (fL)	7.9 (5.5-11.2)	8.2 (6.6-9.7)	7.7 (5.5-11.2)	0.109
>7.58	43 (64.2%)	17 (85%)	26 (55.3%)	**0.026**
≤7.58	24 (35.8%)	3 (15%)	21 (44.7%)	
Neutrophil (10^3/mL)	4.3 (1.33-9.6)	4.7 (2.8-9.6)	3.9 (1.3-7.7)	0.066
>4	37 (55.2%)	15 (75%)	22 (46.8%)	0.059
≤4	30 (44.8%)	5 (25%)	25 (53.2%)	
Lymphocyte (10^3/mL)	2.2 (0.98-3.58)	2.3 (1.0-3.5)	2.1 (0.9-3.5)	0.197
>2.85	8 (11.9%)	6 (30%)	2 (4.3%)	**0.007**
≤2.85	59 (88.1%)	14 (70%)	45 (95.7%)	
Monocyte (10^3/mL)	0.52 (0.27-1.04)	0.62 (0.3-1.0)	0.50 (0.2-0.9)	0.131
>0.539	32 (47.8%)	13 (65%)	19 (40.4%)	0.108
≤0.539	35 (52.2%)	7 (35%)	28 (59.6%)	
NLR	1.9 (0.6-8.3)	2.06 (1.2-8.3)	1.95 (0.6-5.8)	0.468
>1.16	59 (88.1%)	20 (100%)	39 (83%)	0.094
≤1.16	8 (11.9%)	0 (0%)	8 (17%)	
MLR	0.24 (0.11-0.63)	0.25 (0.16-0.63)	0.24 (0.1-0.4)	0.805
>0.15	62 (92.5%)	20 (100%)	42 (89.4%)	0.321
≤0.15	5 (7.5%)	0 (0%)	5 (10.6%)	
PLR	114 (61.28-325)	113 (64.3-248.6)	114 (61.2-325)	0.511
>89.8	16 (23.9%)	7 (35%)	9 (19.1%)	0.213
≤89.8	51 (76.1%)	13 (65%)	38 (80.9%)	
CRP (mg/dL) (n=62)	0.97 (0.15-82.2)	2.95 (0.5-82.2)	0.8 (0.1-26)	**0.001**
>2.7	18 (29%)	12 (60%)	6 (14.3%)	**0.001**
≤2.7	44 (71%)	8 (40%)	36 (85.7%)	
ESR (mm/h) (n=55)	13 (2-67)	16 (2-67)	10 (2-32)	0.121
>13	27 (49.1%)	14 (70%)	13 (37.1%)	**0.026**
≤13	28 (50.9%)	6 (30%)	22 (62.9%)	

BD: Behçet's disease, RAS: Recurrent aphthous stomatitis, MCV: Mean corpuscular volume, RDW: Red cell distribution width, MPV: Mean platelet volume, NLR: Neutrophil/lymphocyte ratio, MLR: Monocyte/lymphocyte ratio, PLR: Platelet/lymphocyte ratio, CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate, [a]p: Student's t-test or Mann-Whitney U test, [b]p: Fisher's exact test, comparison of the distributions according to the cut-off values

Table 3. Logistic regression analyses showing variables associated with the presence of Behçet's disease in patients with recurrent oral ulcerations

Dependent variable	Univariate, (n=67)				Multivariate*, (n=62)			
	OR	95% CI		p	OR	95% CI		p
Sex (male/female)	2.89	0.95	8.82	0.062				
Age (≤37/>37)	**4.20**	**1.08**	**16.30**	**0.038**				
CRP (>2.7/≤2.7) (n=62)	**9.00**	**2.59**	**31.22**	**0.001**	**12.76**	**2.86**	**56.88**	**0.001**
ESR mm/h (>13/≤13)	**3.95**	**1.22**	**12.81**	**0.022**				
RDW (≤14.3/>14.3)	**3.25**	**1.00**	**10.52**	**0.049**				
Hemoglobin (≤14.9/>14.9)	1.88	0.53	6.58	0.326				
MCV (≤88.5/>88.5)	2.04	0.63	6.54	0.233				
Platelet (>253/≤253)	1.65	0.58	4.73	0.352				
Neutrophil (>4/≤4)	**3.41**	**1.07**	**10.91**	**0.039**				
Lymphocyte (>2.85/≤2.85)	**9.64**	**1.75**	**53.26**	**0.009**	**15.24**	**1.77**	**131.31**	**0.013**
Monocyte (>0.539/≤0.539)	2.74	0.92	8.12	0.070				
MPV (>7.58/≤7.58)	**4.58**	**1.18**	**17.75**	**0.028**	**5.61**	**1.11**	**28.42**	**0.037**
PLR (≤89.84/>89.84)	2.27	0.70	7.34	0.169				

*Logistic Regression - Backward Stepwise (Wald)/constant: -3.23 OR: 0.40 p<0.001. OR: Odds ratio, CI: Confidence interval, MCV: Mean corpuscular volume, RDW: Red cell distribution width, MPV: Mean platelet volume, NLR: Neutrophil/lymphocyte ratio, MLR: Monocyte/lymphocyte ratio, PLR: Platelet/lymphocyte ratio, CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate

hemoglobin was decreased in patients with BD compared with the healthy control. Furthermore, NLR and hemoglobin were determined as the indicators of BD in logistic regression analysis[20]. Avci et al.[21] showed that among NLR, MPV and PLR values, NLR was the best predictor of anterior uveitis in BD. Similarly, in another study, both NLR and PLR were significantly higher in patients with BD who have active ocular involvement than in the ones without[22]. In a single center, prospective, case-control study evaluating the difference of hematological markers of patients with BD from patients with RAS, NLR and neutrophil count did not differ between the BD and the RAS groups[23]. Compatible with these results, NLR did not differ between the study groups in our study, while a positive correlation was determined between CRP and NLR in the BD group. Although the neutrophil count was higher in the BD group than in the RAS group, this difference was not statistically significant (p=0.066).

Platelets are suggested to play an essential role in inflammatory reactions and immune response[17]. Jiang et al.[24] demonstrated that PLR was significantly higher in patients with active BD, and positively correlated with BD activity scores. Lee and Song[19] reported that PLR was higher in the BD group than in the control group, although this difference was not statistically significant (SMD, 0.441; 95% CI, -0.025 to 0.907, p=0.063). Despite this, PLR was significantly higher in the active BD group than in the inactive BD group, while it did not differ between the BD group with thrombosis and those without thrombosis[19]. In the study by Turan et al.[23], PLR did not differ between the BD group, RAS group and healthy controls (p=0.943). Similar to Turan's investigation, no significant difference was found when the PLR values between the study groups were compared in our study.

Although previous studies on RA and SLE reported that low MPV values are associated with high disease activity, it was suggested that MPV is more variable than platelet and other blood cell counts, limiting its usage[12]. The meta-analysis by Lee and Song[19]. revealed that MPV was not different between BD groups according to disease activity and the presence or absence of thrombosis. In a study of patients with BD, RAS, and healthy controls, hemoglobin, platelet and CRP levels were not statistically different in patients with BD and RAS compared to controls. Besides, MPV levels and ESR were significantly higher in patients with BD and RAS than in controls (p<0.001). However, laboratory parameters did not differ between the BD and RAS groups. MPV levels were not affected by the disease activity in either of the groups. There was no significant relationship between the MPV and other parameters. In the conclusion, the authors did not recommend MPV value as a predictor of BD[25]. Similarly, Şenel et al.[26] found no significant difference in MPV levels between the BD and RAS groups. Additionally, mean MPV was significantly elevated in the RAS group compared to the control group (9.11±1.01 fL vs. 8.76±1.15 fL, p=0.045)[26]. In our study, increased MPV (>7.58 fL) was related to the BD group with increased CRP level and lymphocyte count. Contrary to these findings, Turan et al.[23] found that MPV value was significantly lower in patients with BD than in healthy controls and RAS patients. Logistic regression analysis distinguished decreased MPV (≤10 fL) and increased RDW (≥13.0%) as predictors of BD. The dissimilarity of these results may be due to some differences such as disease duration and activity, as well as the drug use history of the patients included in the studies, which may affect MPV values.

Although innate immunity is suggested to play a dominant role in BD, adaptive immunity also contributes to the pathogenesis. It is thought that in genetically susceptible patients, exogenous factors such as streptococcus sanguinis and herpes simplex virus trigger both T-cell and innate immune cell activation, resulting in sequential neutrophil activation[16]. The association between innate and adaptive immunity is also considered important in the pathogenesis of RAS. Ruan et al.[27] reported that the percentage of CD4+ T- and B-cells was significantly decreased in RAS patients than in healthy controls while the percentage of CD8+ T- and NK-cells was significantly increased in those compared with healthy controls. Pekiner et al.[28] revealed that CD4+ CD25 T-regulatory cells were higher in both patients with BD and RAS than

in healthy controls, indicating this subtype of T-cells plays a role in the pathogenesis of BD and RAS. Our findings suggest that lymphocyte count elevation above 2.85 $10^3/\mu L$ is more likely to be in patients with BD than those with RAS.

CRP and ESR are acute phase reactants that are demonstrated as indicators for measuring inflammation in BD[29]. Melikoglu and Topkarci[30]. revealed that both CRP and ESR correlated well with total BD Current Activity Form (BDCAF) score of BD patients. They also found that CRP and ESR were significantly higher in BD patients with erythema nodosum, superficial thrombophlebitis and/or arthritis than in patients with BD without these manifestations[30]. In our study, the frequency of patients with increased CRP (>2.7 mg/dL) and ESR (>13 mm/h) was significantly higher in the BD group than in the RAS group. In logistic regression analyses, a CRP value higher than 2.7 mg/dL was likely to be in patients with BD compared to those with RAS. Additionally, CRP was correlated with ESR and NLR in the BD group. Although we could not perform the BDCAF, the most used activity score in BD, this result is probably due to the mild to moderate disease activity in patients who just fulfilled the BD criteria.

Study Limitations

The most important limitations of this study are the cross-sectional design, relatively small number of patients and absence of the healthy control group. The results should be interpreted by taking this into account because the small number of cases in our study may not be sufficient to detect a significant difference between the groups. However, evaluating patients with newly diagnosed BD in our study may shed light on further studies on this subject. Additionally, it would be more explanatory to show the change in hematological parameters by serial laboratory measurements correlated with accompanying manifestations of BD.

Conclusion

Although there are a few studies regarding the predictive role of the hematological parameters distinguishing BD from RAS, to our knowledge, our study is the first to compare the findings between newly diagnosed BD patients and RAS patients.

Besides increased CRP levels, which are already known as an indicator of inflammation in BD, MPV level and lymphocyte count were found to be higher in patients with BD compared to those with RAS. Further extensive prospective longitudinal studies with the healthy control group and serial measurements of hematological parameters are needed to confirm these findings.

Ethics

Ethics Committee Approval: Clinical data were assessed after the approval of the Bilecik State Hospital Local Ethics Committee (approval number: 2020/001, date: 05.02.2020).

Informed Consent: It was obtained.

Authorship Contributions

Concept: C.A., S.A., Ö.Ö., Design: C.A., S.A., Ö.Ö., Data Collection or Processing: C.A., Analysis or Interpretation: C.A., S.A., Ö.Ö., Literature Search: C.A., S.A., Writing: C.A., S.A., Ö.Ö.

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References

1. Slebioda Z, Szponar E, Kowalska A: Etiopathogenesis of recurrent aphthous stomatitis and the role of immunologic aspects: literature review. Arch Immunol Ther Exp (Warsz). 2014;62:205-15.
2. Bulur I, Onder M: Behçet disease: New aspects. Clin Dermatol. 2017;35:421-34.
3. Alpsoy E: Behçet's disease: A comprehensive review with a focus on epidemiology, etiology and clinical features, and management of mucocutaneous lesions. J Dermatol. 2016;43:620-32.
4. Cui RZ, Bruce AJ, Rogers RS 3rd: Recurrent aphthous stomatitis. Clin Dermatol. 2016;34:475-81.
5. Bang D, Hur W, Lee ES, Lee S: Prognosis and clinical relevance of recurrent oral ulceration in Behçet's disease. J Dermatol. 1995;22:926-9.
6. Oh SH, Han EC, Lee JH, Bang D: Comparison of the clinical features of recurrent aphthous stomatitis and Behçet's disease. Clin Exp Dermatol. 2009;34:e208-12.
7. Krause I, Mader R, Sulkes J, et al.: Behçet's disease in Israel: the influence of ethnic origin on disease expression and severity. J Rheumatol. 2001;28:1033-6.
8. Rogers RS 3rd: Recurrent aphthous stomatitis in the diagnosis of Behçet's disease. Yonsei Med J. 1997;38:370-9.
9. Pekiner FN, Aytugar E, Demirel GY, Borahan MO: HLA-A, B (Class I) and HLA-DR, DQ (Class II) antigens in Turkish patients with recurrent aphthous ulceration and Behçet's disease. Med Princ Pract. 2013;22:464-8.
10. Dalghous AM, Freysdottir J, Fortune F: Expression of cytokines, chemokines, and chemokine receptors in oral ulcers of patients with Behcet's disease (BD) and recurrent aphthous stomatitis is Th1-associated, although Th2-association is also observed in patients with BD. Scand J Rheumatol. 2006;35:472-5.
11. Shenavandeh S, Sadeghi SMK, Aflaki E: Pathergy test with a 23G needle with and without self-saliva in patients with Behçet's disease, recurrent aphthous stomatitis and control group compared to the 20G test. Reumatologia. 2021;59:302-8.
12. Gasparyan AY, Ayvazyan L, Mukanova U, Yessirkepov M, Kitas GD: The platelet-to-lymphocyte ratio as an inflammatory marker in rheumatic diseases. Ann Lab Med. 2019;39:345-57.
13. Criteria for diagnosis of Behçet's disease. International Study Group for Behçet's Disease. Lancet. 1990;335:1078-80.
14. Djaballah-Ider F, Touil-Boukoffa C: Effect of combined colchicine-corticosteroid treatment on neutrophil/lymphocyte ratio: a predictive marker in Behçet disease activity. Inflammopharmacology. 2020;28:819-29.
15. Seçkin HY, Bütün I, Baş Y, Takcı Z, Kalkan G: Effects of colchicine treatment on mean platelet volume and the inflammatory markers in recurrent aphthous stomatitis. J Dermatolog Treat. 2016;27:389-91.
16. Perazzio Perazzio SF, Andrade LEC, de Souza AWS: Understanding Behçet's Disease in the Context of Innate Immunity Activation. Front Immunol. 2020;11:586558.
17. Tezcan D, Körez MK, Gülcemal S, Hakbilen S, Akdağ T, Yılmaz S: Evaluation of diagnostic performance of haematological parameters in Behçet's disease. Int J Clin Pract. 2021;75:e14638.
18. Hammad M, Shehata OZ, Abdel-Latif SM, El-Din AMM: Neutrophil/lymphocyte ratio and platelet/lymphocyte ratio in Behçet's disease: which and when to use? Clin Rheumatol. 2018;37:2811-7.
19. Lee YH, Song GG: Neutrophil-to-lymphocyte ratio, mean platelet volume and platelet-to-lymphocyte ratio in Behçet's disease and their correlation with disease activity: a meta-analysis. Int J Rheum Dis. 2018;21:2180-7.
20. Zhang Z, Su Q, Zhang L, Yang Z, Qiu Y, Mo W: Diagnostic value of hemoglobin and neutrophil-to-lymphocyte ratio in Behcet Disease. Medicine (Baltimore). 2019;98:e18443.

21. Avci A, Avci D, Erden F, et al.: Can we use the neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, and mean platelet volume values for the diagnosis of anterior uveitis in patients with Behcet's disease? Ther Clin Risk Manag. 2017;13:881-6.
22. Shadmanfar S, Masoumi M, Davatchi F, et al.: Correlation of clinical signs and symptoms of Behçet's disease with platelet-to-lymphocyte ratio (PLR) and neutrophil-to-lymphocyte ratio (NLR). Immunol Res. 2021;69:363-71.
23. Turan Ç, Metin N, Utlu Z, Tezcan D: Mean platelet volume as a predictor in the differentiation of Behçet's disease from recurrent aphthous stomatitis - a single centre, prospective, case-control study. Int J Clin Pract. 2021;75:e14866.
24. Jiang Y, Zang M, Li S: Serum PLR and LMR in Behçet's disease: can they show the disease activity? Medicine (Baltimore). 2017;96:e6981.
25. Ekiz O, Balta I, Sen BB, Rifaioglu EN, Ergin C, Balta S, Demirkol S: Mean platelet volume in recurrent aphthous stomatitis and Behçet disease. Angiology. 2014;65:161-5.
26. Şenel E, Acar B, Demir E: Mean Platelet Volume: A reliable marker of inflammation in recurrent apthous stomatitis and Behçet disease? Indian Dermatol Online J. 2017;8:468-70.
27. Ruan HH, Li GY, Duan N, et al.: Frequencies of abnormal humoral and cellular immune component levels in peripheral blood of patients with recurrent aphthous ulceration. J Dent Sci. 2018;13:124-30.
28. Pekiner FN, Aytugar E, Demirel GY, Borahan MO: Interleukin-2, interleukin-6 and T regulatory cells in peripheral blood of patients with Behçet's disease and recurrent aphthous ulcerations. J Oral Pathol Med. 2012;41:73-9.
29. Hou CC, Guan JL: Risk factors of disease activity in patients with Behçet's syndrome. Clin Rheumatol. 2021;40:1465-71.
30. Melikoglu M, Topkarci Z: Is there a relation between clinical disease activity and acute phase response in Behcet's disease? Int J Dermatol. 2014;53: 250-4.