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Original Article

Could Mean Platelet Volume Be Used as A Marker for Oral Aphthae and Activity of Behçet's Disease?

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Abstract

Objective: Behçet's disease is a common inflammatory disease in our country. We aimed to determine whether mean platelet volume can be used as a marker for oral aphthae and the activity of Behçet's disease.

Methods: Between 04/01/2010 and 30/07/2010, 78 patients from the Okmeydanı Training and Research Hospital Dermatology Clinic were retrospectively enrolled in this study, of which 15 patients had active Behçet's disease and 37 had inactive Behçet's disease that were diagnosed according to the International Criteria for Behçet's Disease; 26 control patients without any inflammatory disease were also evaluated. Mean platelet volume and laboratory indicators of inflammation were compared between the patients and control groups.

Results: There were no significant differences in the mean platelet volume values between the active Behçet's disease group, inactive Behçet's disease group, and control group (p=0.678). Furthermore, there were no significant differences in the mean platelet volume values between patients with oral aphthae, patients without oral aphthae, and control patients (p=0.637).

Conclusion: Our results demonstrate that mean platelet volume values cannot be used as a marker for oral aphthae and activity of Behçet's disease. However, immunosuppressive agents, such as colchicine and corticosteroids that are used in treating Behçet's disease, could affect the mean platelet volume values in active or inactive Behçet's disease by suppressing the inflammatory process. Therefore, we believe that the evaluation of the mean platelet volume values in large-scale studies that include patients with newly diagnosed Behçet's disease, which have not been treated, would be useful.

Keywords: Behçet's disease, platelet, inflammation

Introduction

Behçet's disease is an inflammatory vasculitis that presents with immunological, endothelial, and neutrophilic changes (1). Although the etiopathogenesis of Behçet's disease, which is an immunoinflammatory disorder, is not exactly known, it is suggested that genetics, infection, immune complexes, antibodies, and oxidative stress are among the causes of this disease (2-5). There is no laboratory finding that is specific to the disease. Mild anemia in chronic disease, sedimentation, and increased C-reactive protein (CRP) levels can be found. Moreover, cryoglobulinemia, leukocytosis, and eosinophilia can be observed (6).

Behçet's syndrome is a multisystem disease that can be diagnosed by the presence of at least two of recurrent genital ulceration, typical eye lesions, typical cutaneous lesions, and a positive pathergy test, in addition to recurrent oral aphthous ulceration. This definition was made by an international study group in 1990 and is accepted by many researchers at present (7).

Behçet's disease can be seen worldwide. However, various geographical differences are observed (8). It is seen in the Middle East and Asia, particularly in Turkey, Japan, Korea, and Mediterranean countries. The onset of the disease often occurs between 20 and 40 years (9). Its prevalence is 1/300,000 in Europe, 1/10,000 in Japan, and 8–37/10,000 in Turkey (10).

Oral aphthae are usually the first sign of the disease. A typical lesion is painful, 1–3 cm in diameter, and has a yellow fibrinous base. Aphthae mostly heal without leaving any scar and recur once or several times in a month (11).

Platelets basically play a role in thrombosis and hemostasis. However, recent studies have revealed that platelets also have a role in infection and inflammation (12). It has been revealed that chemokines released from activated platelet membranes have important roles in immune response. Also, it has been reported that these released chemokines take part in the initial immune response as acute-phase reactants; they act on neutrophils, granulocytes, and monocytes and directly display antimicrobial effects (13, 14). When a platelet is activated and releases inflammatory factors such as chemokines and cytokines, the size of the platelet increases. In other words, an increased mean platelet volume (MPV) is an indicator of activated platelets (15). MPV is

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determined as a part of the routine complete blood count in complete blood count analyzers (16, 17). Some studies have revealed that MPV can be used as a marker of inflammation in various inflammatory diseases. In the literature, there are some studies that report that MPV shows a positive or negative correlation with inflammatory activity (18-20).

In this study, the aim was to investigate whether MPV values could be used as a marker of oral aphthae and disease activity in patients with Behçet's disease, which is an inflammatory disorder commonly seen in Turkey.

Methods

In this retrospective study, 52 patients with Behçet's syndrome (15 in the active and 37 in the inactive stage), who were diagnosed in accordance with the International Study Group diagnostic criteria in Clinic of Dermotology, Okmeydanı Training and Research Hospital between January 4, 2010 and July 30, 2010 and 26 patients without any inflammatory disease (control group) were included (21).

Patients who had at least two of the findings of genital ulceration, cutaneous signs such as erythema nodosum, arthritis, and eye involvement, in addition to oral aphthae, were determined to be in the active stage (22, 23). The other patients were determined to be in the inactive period. Patients with another inflammatory disorder or malignancy were excluded from the study.

Patients were divided into two groups: patients with Behçet's disease and a control group. The Behçet's disease group was divided into two subgroups, which corresponded to the active and inactive stages, in the statistical evaluation. Then, in terms of the presence of oral aphthae, the patients were divided into two groups: Behçet's disease patients with and without oral aphthae. The MPV, CRP level, fibrinogen level, sedimentation rate, leukocyte count (WBC), and platelet count (PLT), which are laboratory markers of inflammation, were statistically evaluated in the patient and control groups. The PLT and MPV values of the patient and control groups were measured with an ADVIA 120 hematology device, ferritin levels by immunochemiluminescence measurement in a Beckman Coulter DXI 800 hormone autoanalyzer, fibrinogen levels by a light detection method with multiple wavelengths in a Trinity Biotech MDA II coagulation autoanalyzer, the erythrocyte sedimentation rate (ESR) with an ERLINE AR device, and CRP levels by a nephelometric method with a BN II device.

Statistical analysis

Statistical analyses were performed with MedCalc software (MedCalc Software, Mariakerke, Belgium). The suitability of continuous variables for normal distribution was investigated by the Kolmogorov–Smirnov test. Variables with Gaussian distribution were presented as the mean±SD and variables with non-Gaussian distributions were presented as the median (interquartile range). Student's t-test was used for comparing mean values between two groups. The Mann–Whitney U test was employed for the comparison of median values between two groups. On the other hand, for more than two groups, one-way analysis of variance (ANOVA) (post hoc analyses with Tukey's or Tamhane's T2 tests) and the Kruskal–Wallis test (post hoc analyses with the Mann–Whitney U test; statistical significance level of $p<0.016$) were used for comparing mean values and median values, respectively. Correlation between variables was assessed by the Spearman correlation coefficient (r_s) and Pearson correlation coefficient (r). Moreover, Fisher's exact test was used for comparing observed and expected values. Statistical significance was defined to occur at a value of $p<0.05$ (two-tailed).

Results

Between the control group and Behçet's disease group, the mean values of MPV, PLT, and WBC and median ferritin levels were not statistically significantly different (Table 1). However, the median ESR ($p=0.044$), median CRP levels ($p<0.0001$), and mean fibrinogen levels ($p<0.0001$) were significantly higher in the Behçet's disease group than in the control group. Considering the distributions of CRP levels in the control and patient groups, the values of skewness (control group: 3.4; patient group: 2.9) and kurtosis (control group: 12.1; patient group: 8.9) were high. Therefore, a second evaluation was performed for CRP levels according to a 5 mg/L cut-off value, and the frequency of individuals with CRP levels of ≥5 mg/L was found to be significantly higher in the Behçet's disease group than in the control group ($p=0.018$).

The mean values of MPV, PLT, and WBC were not significantly different between the control group and the Behçet's disease inactive and active patient groups (Table 2). In post hoc comparisons performed for ESR and fibrinogen, CRP, and ferritin levels, which were statistically different between the three groups, the mean fibrinogen level was significantly higher in the Behçet's disease active group than in the control group ($p<0.0001$); the median value of ESR was significantly higher in the Behçet's disease active group than in the control group ($p<0.01$); the median ferritin level was significantly higher in the Behçet's disease active group than in the control group ($p<0.01$); the median CRP level was significantly higher in the Behçet's disease active group than in the control group ($p<0.0001$); and the median CRP level was significantly higher in the Behçet's disease inactive group than in the control group ($p<0.01$).

There was no statistically significant difference between the control group and the Behçet's disease groups with and without oral aphthae in terms of the mean values of MPV, PLT, and WBC and the median values of ESR and ferritin levels (Table 3). In post hoc comparisons performed for fibrinogen and CRP levels, which revealed statistically significant differences between the three groups, the

Table 1. Comparison of MPV, PLT, WBC, ESR, fibrinogen, CRP, and ferritin levels in Behçet's disease group and control group

	Control group (n=26)	Behçet's disease group (n=52)	p
MPV (fL)	7.7±1.0	7.9±1.1	0.364
PLT (×10³/μL)	259.8±80.2	243.5±59.1	0.311
WBC (×10³/μL)	6.9±1.7	7.1±2.5	0.658
ESR (mm/h)	14 (9-27)	21 (12-34)	0.044
Fibrinogen (mg/dL)	265.1±61.6	337.1±110.4	<0.0001
CRP (mg/L)	3.27 (3.22-3.27)	3.30 (3.30-9.40)	<0.0001
CRP ≥5 mg/L (%)	11.5% (n=3)	38.5% (n=20)	0.0180
Ferritin (ng/mL)	24.9 (5.9-51.9)	23.3 (12.0-46.2)	0.589

MPV: mean platelet volume; PLT: platelet count; WBC: leukocyte count; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein

Table 2.Comparison of MPV, PLT, WBC, ESR, fibrinogen, CRP, and ferritin levels in Behçet's disease inactive group, Behçet's disease active group, and control group

	Control group (n=26)	Behçet's disease inactive group (n=37)	Behçet's disease active group (n=15)	p
MPV (fL)	7.7±1.0	8.0±1.1	7.8±1.1	0.678
PLT (×10³/µL)	259.8±80.2	235.0±58.7	264.4±56.6	0.240
WBC (×10³/µL)	6.9±1.7	7.0±2.7	7.3±2.0	0.796
ESR (mm/h)	14 (9-27)	16 (12-32)	25 (20-53)a	0.020
Fibrinogen (mg/dL)	265.1±61.6	313.5±94.4	395.2±128.2b	<0.001
CRP (mg/L)	3.27 (3.22-3.27)	3.30 (3.30-9.20)a	6.10 (3.30-14.30)b	<0.0001
CRP ≥5 mg/L (%)	11.5% (n=3)	32.4% (n=12)	53.3% (n=8)	
Ferritin (ng/mL)	24.9 (5.9-51.9)	17.0 (7.3-35.0)	44.9 (26.5-64.9)c	0.024

MPV: mean platelet volume; PLT: platelet count; WBC: leukocyte count; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein

In post hoc multiple comparisons performed with the Mann–Whitney U test after the Kruskal–Wallis H test, statistical significance was defined to occur at a value of p<0.016.

[a]p<0.01 according to the control group

[b]p<0.0001 according to the control group

[c]p<0.01 according to the Behçet's disease inactive group

Table 3. Comparison of MPV, PLT, WBC, ESR, fibrinogen, CRP, and ferritin levels in the Behçet's disease group without oral aphthae, Behçet's disease group with oral aphthae, and control group

	Control group (n=26)	Behçet's disease group without oral aphthae (n=26)	Behçet's disease group with oral aphthae (n=26)	p
MPV (fL)	7.7±1.0	7.8±0.9	8.0±1.3	0.637
PLT (×10³/µL)	259.8±80.2	242.6±62.2	244.4±57.0	0.820
WBC (×10³/µL)	6.9±1.7	6.7±1.6	7.5±3.1	0.741
ESR (mm/h)	14 (9–27)	19 (13–30)	21 (12–35)	0.108
Fibrinogen (mg/dL)	265.1±61.6	329.9±100.5	344.3±121.1[b]	0.008
CRP (mg/L)	3.27 (3.22–3.27)	3.30 (3.30–9.73)[a]	3.60 (3.30–9.43)[b]	<0.001
CRP ≥5 mg/L (%)	11.5% (n=3)	34.6% (n=9)	42.3% (n=11)	
Ferritin (ng/mL)	24.9 (5.9–51.9)	17.0 (11.1–37.6)	31.8 (13.0–50.7)	0.551

MPV: mean platelet volume; PLT: platelet count; WBC: leukocyte count; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein

In post hoc multiple comparisons performed with the Mann–Whitney U test after the Kruskal–Wallis H test, statistical significance was defined to occur at a value of p<0.016.

[a]p<0.01 according to the control group

[b]p<0.0001 according to the control group

mean fibrinogen level was found to be significantly higher in the patient group with Behçet's oral aphthae than in the control group (p<0.0001); the median CRP level was significantly higher in the patient group with Behçet's oral aphthae than in the control group (p<0.0001); and the median CRP level was significantly higher in the patient group without Behçet's oral aphthae than in the control group (p<0.01).

Discussion

In our study, it was found that CRP levels were significantly higher in all Behçet's disease patients than in the control group patients. Our findings confirm that inflammation plays a role in the pathology of Behçet's disease and are consistent with the CRP results of Sandıkcı et al. (5). The values of fibrinogen levels and sedimentation rate, which are other markers of inflammation, were revealed to be higher in all Behçet's disease patients than in the control group patients. This supports the role of inflammation in Behçet's disease.

In our study, MPV values were statistically compared between the control group and the patient group with Behçet's disease, and no statistically significant difference was found between the groups (Table 1). Ekiz et al. (24) reported in their study that MPV values were significantly higher in the Behçet's disease group than in the control group. Koçer et al. (25) conducted a study on patients with ankylosing spondylitis, which is an inflammatory disease, and detected that MPV values were significantly higher in the patient group than in the control group. Our findings were inconsistent with those in these studies. We suggest that the study should be repeated with groups that include more patients who have recently been diagnosed and have never been given any drug therapy. Our study might have been different from other studies owing to the fact that our patients used immunosuppressive drugs such as colchicine and corticosteroids and the durations of disease were different.

Our study compared MPV values between the control group and the Behçet's disease groups with inactive and active patients statistically and no statistically significant difference was found between the groups (Table 2). It was concluded that MPV alone could not be used as a marker for disease activity. In the study of Ekiz et al. (24), in the patient group with Behçet's disease, they reported that MPV values were not affected by disease activity and MPV could not be used as a marker for disease. Özuğuz et al. (26) did not find a

significant difference between active and inactive Behçet's disease patients in terms of MPV values. Our findings were consistent with these findings.

Uzerk Kibar et al. (27) reported significantly higher MPV values in the group with active Behçet's disease than in the group with inactive Behçet's disease and stated that MPV could be an independent indicator of disease activity. In another study on patients with Behçet's disease, Ryu et al. (28) reported significantly lower MPV values in the group with active Behçet's disease than in the group with inactive Behçet's disease.

Similarly to this finding, in the study of Koçer et al. (25) on patients with ankylosing spondylitis, they found that MPV values were significantly lower in the active patient group than in the inactive patient group. Our findings were inconsistent with theirs. In the literature, MPV levels were found to be lower in patients with rheumatoid arthritis and it was stated that this situation might have been associated with extensive consumption of platelets in the vessel walls and synovial membranes. Large platelets are more reactive; their granular contents are more extensive compared with those of small platelets and they produce more cytokines and thromboxane A2 (29). Moreover, it has been suggested that the excessive production of proinflammatory cytokines and acute-phase reactants could affect the platelet production process and lead to the release of small-volume platelets and thus a reduction in platelet size (30). This inverse relationship, which is frequently observed between PLT and MPV in physiological and pathological situations, keeps the platelet mass steady and provides hemostasis (31). It has been reported that via this inverse relationship platelet production is stimulated and PLT in the circulation increases, but large-volume platelets migrate to the region of inflammation and are used in this region. Furthermore, some factors such as defective thrombopoiesis, increased degradation, and platelets that become larger in an environment rich in reactive substances can also affect the relationship between PLT and MPV (32).

In our study, MPV values were statistically compared between the control group and the Behçet's disease groups with and without oral aphthae and no statistically significant difference was detected (Table 3). Based on these data, we found that MPV alone could not be used as a marker of oral aphthae. Because no study that made similar comparisons was found in a literature review, it was impossible to confirm our results directly.

Inflammatory diseases can cause anemia and thrombocytosis (33, 34). It is estimated that in particular thrombocytosis occurs in association with proinflammatory cytokines and some growth factors (33-36). Proinflammatory cytokines, especially interleukin-6 (IL-6), play an important role in the pathogenesis of inflammatory arthritis (34-36). Furthermore, it has been suggested that increased IL-6 levels can stimulate platelet production and cause the release of large-volume platelets from bone marrow (37). Therefore, cytokine levels should be measured in further studies and it should be kept in mind that there may be different mechanisms that can create differences between studies.

Conclusion

Studies on MPV in Behçet's disease have revealed conflicting results. In this study, we detected that MPV values that were obtained from complete blood count samples of patients with Behçet's disease, which is an inflammatory disease common in Turkey, could not be used as a marker of oral aphthae and disease activity in these patients.

We suggest that further studies that measure cytokine levels and include a larger population with currently diagnosed patients who have not been given any drug treatment must be conducted because immunosuppressive drugs such as colchicine and corticosteroids, which are used by Behçet's disease patients, can affect inflammatory processes and change the MPV levels of these patients in the active or inactive stages.

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Informed Consent: Written informed consent was not received due to the retrospective nature of this study.

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