THE RELATION BETWEEN DISEASE ACTIVITY, FINDINGS AND MEAN PLATELET VOLUME IN BEHÇET'S DISEASE

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ABSTRACT

Introduction: In Behçet's disease (BD), during recurrent inflammatory attacks, various vasculitic involvements may be seen in different systems. It is difficult to measure disease activity in these patients, because disease presents with attacks and relapses and there is no specific laboratory test that encompasses all findings of disease. The aim of the present study was to investigate the relation between clinical activity of BD disease and mean platelet volume (MPV).

Methods: 200 patients meeting 1990 classification criteria of International Behçet's disease Study Group and who were followed between October 2011 and June 2012 in Multidisciplinary BD outpatient clinic were included in the study. Files of BD patients in the archive of BD outpatient clinic and data recorded in Electronic Health Records were examined.

Results: Patients were divided into two groups, patients with or without active disease were named group 1 and group 2, respectively. In all BD patients, independently from disease activity, no significant difference was found between the patients with a history of thrombosis and those without it with respect to MPV (9.12 vs 8.89 fl, respectively, p=0.117). In patients with active disease, MPV values were significantly higher than those without active disease (9.43 vs 8.41 fl, respectively, p<0.05). Among patients with active disease (group 1), no significant difference was found in MPV values of those with a history of thrombosis and those without it (9.47 vs 9.27 fl, p>0.05).

Conclusion: The higher MPV values in BD patients seem to be an independent factor predicting disease activity.

Key words: Vasculitis, Behçet's disease, mean platelet volume (MPV), Clinical aspects.

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Introduction

Behçet’s Disease (BD) was originally defined by a dermatologist Prof. Dr. Hulusi Behçet in 1937 as a tri symptom complex characterized by recurrent oral and genital aphthous ulcers and uveitis with hypopyon(1,2). In addition to these symptoms, arthritis, skin lesions, vasculopathy, enteropathy and involvement of central nervous system reflects the systemic inflammatory nature of the disease. Although significant advances have been made in elucidating the pathogenesis of disease, it has still not been completely understood. The disease courses with remission and relapse periods. There is neither a pathognomonic laboratory finding of the disease nor a specific marker reflecting disease activity.

It has been reported that, mean platelet volume (MPV) which is nowadays a parameter of intense interest, is associated with cardiovascular risk factors, has prognostic value in acute coronary syndromes and increases in parallel to the severity of ischemic cerebrovascular events(3,4). It has been suggested in many studies that MPV has an important role as a marker of inflammation and that it reflects disease activity in chronic inflammatory disease and efficacy of anti-inflamm-
flammatory treatment. Since the disease activity has been related to MPV in many inflammatory diseases such as rheumatoid arthritis (RA), ankylosing spondylitis (AS), inflammatory bowel diseases, and familial Mediterranean fever (FMF), the question raises whether this easily obtainable laboratory finding has any predictive value for disease activity in BD. The aim of the present study was to evaluate the relation between clinical activity of BD and MPV.

**Materials and methods**

Present study was conducted between October 2011 and June 2012. 200 patients who were previously or newly diagnosed as BD and followed in Ankara University Faculty of Medicine Rheumatology Department Outpatient clinic and Multidisciplinary BD outpatient clinic were included in the study.

The patients with another systemic inflammatory or autoimmune disease, hypertension, diabetes mellitus, coronary artery disease, heart valve disease, treated with anticoagulants, antihyperlipidemic and antihypertensive drugs, who have liver and renal failure, aminotransferase levels two fold higher than normal levels, hematological disease, acute or chronic infection and malignancy were excluded from the study.

Files of patients in Multidisciplinary BD archive and data recorded in hospital based electronic medical records were examined. Symptoms present at the time of referral to outpatient clinic, examination findings, drug use history, systemic involvement, and radiological investigations were evaluated.

Based upon physical examination at the outpatient clinic and multisystemic evaluation, patients who have at least two of the symptoms and signs of oral ulcer, genital ulcer, active uveitis, active arthritis, acute thrombophlebitis, and acute deep vein thrombosis (DVT) were considered to have active disease while those without these findings or who have only oral ulcer were included in inactive disease group and the pulmonary artery aneurysm with a diagnosis, neurobehçet's disease diagnosed patients under treatment and activity meets the criteria that the inactive group were evaluated.

Blood samples drawn from patients were evaluated at Ankara University, Faculty of Medicine, İbni Sina hospital central laboratory. For evaluation of MPV, whole blood samples were analyzed with Beckman-Coulter LH 780 whole blood counting device. In this device, electrical impedance method is used. The erythrocyte sedimentation rate (ESR), C- reactive protein (CRP), the number of leukocytes and thrombocytes and MPV measured in samples were recorded.

**Statistical evaluation**

In the analysis of the data, Statistical Packages for the Social Sciences (SPSS)15 program was used. The distribution of data for normality was evaluated. Descriptive statistics of the variables that distributed normally were expressed as mean ± standard deviation and that of variables that were not normally distributed as median (minimum-maximum). For two group comparisons, t test, for variables distributed normally, and Mann Whitney U test, for those not normally distributed, were used. For the comparison of more than two groups, Spearman correlation constant was used. The difference between categorical variables in patient groups was investigated with chi square (x2) test. ROC curve analysis was used to find out if MPV value could discriminate between groups. In order to evaluate independent factors influencing the disease activity, logistic regression analysis was used.

P value of p<0.05 was considered statistically significant.

**Results**

200 patients (123 female and 77 male) meeting 1990 classification criteria of International BD Study Group were included in the present study. Patients were divided into groups of active disease (group I) and inactive disease (group II). There were 100 patients in each group. Sex distribution in groups was as follows: In group I, frequency of female patients was 48% (n=59), and that of male patients 53.2% (n=41). In group II, the rate of female patients was 52% (n=64), and that of male patients 46.8% (n=36). No significant difference was found between patient groups in terms of sex distribution (p=0.467). Mean age in group I was 37.5 (min: 18-max: 66) and mean age in group II was 41.5 (min: 21-max: 64). Statistically significant difference was found between two groups in terms of age distribution (p<0.008), patients with active disease usually being younger (table 1). When systemic involvement was evaluated, it was established that all patients had oral aphthous ulcer, 82% had genital ulcer, 70.5% papulopustular lesion, 57%
erythema nodosum, 10% arthritis, 62.5% arthralgia, 38% eye involvement, 10.5% DVT history, 5% history of thrombophlebitis, 3% gastrointestinal system (GIS) involvement, 5.5% neurological involvement, 2.5% pulmonary involvement and 28.5% positive pathergy test results (figure 1).

The relation between ESR, CRP, the number of leukocytes and thrombocytes and disease activity was evaluated. Mean value of ESR was: 11.00 (min:2-max: 35) mm/hour for inactive patients while it was 20.50 (min:2-max: 103) mm/hour for active patients. Statistically significant relation was found between disease activity and ESR values (p<0.001). Mean CRP value was 1.365 (min:0.742-max:14.4) pg/ml in inactive patients while it was 4.70 (min:0.742-max:150) pg/ml in active patients. Statistically significant relation was found between disease activity and CRP values (p<0.001).

Mean number of leukocytes was 7100 (min:4000-max:12900) in inactive patients while it was 7700 (min:4600-max:15700) in active patients. Mean values of leukocytes were within the normal range, but statistically significant relation was found between disease activity and the number of leukocytes (p=0.001).

Mean number of thrombocytes in inactive patients was 257000 (minimum:153000- maximum:471000) while it was 240000 (min:150000-max:484000) in active patients. Although the mean number of thrombocytes was within the normal range, statistically significant relation was found between disease activity and number of thrombocytes (p=0.001). It was established that the number of thrombocytes was lower in the presence of active disease.

The relation between disease activity and MPV was also evaluated. Mean MPV value was 8.4 (min:6.5-max:10.8) fL in inactive patients while it was 9.4 (min:7.5-max:13.1) fL in active patients. Statistically significant relation was found between predicting disease activity and MPV (p<0.001) (table 2). As it had discriminatory characteristics according to ROC analysis, cut off value for MPV was determined to be >8.45 fL (sensitivity 92%, specificity 55%).

In patients, correlation between ESR, CRP and the number of leukocytes and thrombocytes and MPV was evaluated. Accordingly, no correlation was found between MPV and ESR and the number of leukocytes. (p=0.164 and p= 0.943, respectively) However, correlation was found between MPV, CRP, and the number of thrombocytes. The correlation analysis between MPV and CRP yielded the value of p<0.001 (r=0.251), and there was a negative correlation between MPV and the number of thrombocytes (p<0.001, r=-0.369)

In all patients, the history of thrombosis was compared with MPV irrespective of disease activity. MPV was 8.8 (min:8.2-max:10.5) fL in patients with history of thrombosis while it was 8.8 (min:6.5-max:13.1) fL in those without a history of thrombosis. No significant difference was found between patients who have history of thrombosis and those who do not have it with respect to MPV (p=0.117).
In Group I (active patients), the relation between the history of thrombosis and MPV was investigated and mean MPV was found to be: 9.35 (min:8.2- max:10.5) fL, while it was 9.20 (min:7.5- max:13.1) fL in those without an history of thrombosis. No significant difference was found between those with and without history of thrombosis in group I with regard to MPV. (p=0.553). When the same comparison was made in Group II (inactive patients), mean MPV was found to be 8.75 (min:6.2-max:10.1) IL in those with a history of thrombosis while it was 8.30 (min:6.5- max:10.8) fL in those without a history of thrombosis. Namely, statistically significant difference was found between patients with a history of thrombosis and those without it with respect to MPV in Group II. (p=0.024).

Similarly, patients with a history of ocular involvement and those without it were compared in terms of MPV. Mean MPV was found to be 8.6 (min:6.6-max:11.4) fL in those with ocular involvement and 8.85 (min:6.5-max:13.1) fL in those without ocular involvement. No significant difference was found between these subgroups with regard to MPV (p=0.820).

Patients with a history of arthritis associated with BD and those who do not have such a history were compared in terms of MPV values. Mean MPV was 9.55 (min:7.9- max:10.8) in patients with history of arthritis while it was 8.80(6.5-13.3) in those without a history of arthritis. Statistically significant difference was found between groups in terms of MPV (p=0.019). When regression analysis was carried out, it was found that erythema nodosum, papulo-pustular lesion, ESR, CRP, MPV and oral aphthous ulcers were independent factors indetermining disease activity (table 3).

![Table 3: Logistic regression analysis results.](image)

*Statistically significant

**Discussion**

In the present study, when the relation between ESR and CRP and disease activity was evaluated, it was established that ESR and CRP were higher in the presence of active disease. (respectively p<0.001 and p<0.001). High levels of ESR and CRP, which are acute phase proteins known to increase in conditions in which inflammatory response is triggered, is an expected finding in the presence of clinical disease. In addition, the number of leukocytes was found to be higher in the presence of disease activity. The mean number of thrombocytes was found to be within normal range, but in active disease they were observed to be lower. (p=0.001 and p=0.001); In addition, while positive correlation was found between MPV and CRP value, negative correlation was found between MPV and the number of thrombocytes. (Respectively p<0.001, r = 0.251 and p<0.001, r - 0.369). Negative correlation between MPV and the number of thrombocytes was demonstrated in previous studies(17, 18). This relation is frequently observed in inflammatory disease. It is thought that in inflammatory diseases the number of thrombocytes in circulation rises with increased thrombocyte production; reactive and large thrombocytes are transferred to inflammation regions where they are consumed rapidly.

There are two previous studies evaluating the relation between MPV and disease activity in BD(19,20). In the study of Karabudak et al in 2008, comparing 58 Behçet’s Disease patients with 30 healthy controls, found that MPV was higher in BD patients, but the difference was not statistically significant and no association was established between disease activity and MPV values(19).

In the study of Açikgöz et al in 2010, 60 BD patients were compared with 40 healthy controls and MPV value was found to be significantly higher in patients with BD (p<0.001). In the same study, when BD patients were divided into those with and without thrombosis, MPV was found to be higher in thrombosis group (p<0.05). However, in the comparison between active and inactive patients, no significant difference was found with respect to MPV (p=0.601). In this study, it was suggested that high MPV in BD patients points to the increase in the tendency to thrombocyte aggregation and that, in support of this, MPV is higher in patients with history of thrombosis(20). Small sample size was one of the limitations of the study.

In the present study, it was aimed to evaluate whether MPV has a role in predicting disease activity as an inflammatory marker. According to the findings of the study, a statistically significant relation was found between disease activity and MPV.
MPV correlated with disease activity evaluated seen in MPV value. In addition, it was stated that and anti-TNF treatment) significant reduction was six months of treatment (conventional treatment MPV value was higher in AS patients. Following compared prior to treatment, it was observed that increase occurred in MPV values of RA and AS patients were evaluated again two months after control group. (p<0.001 and p<0.001). When patients with history of arthritis was lower during an attack of FMF than an attack free period. (p=0.00) Atherosclerosis risk was suggested to be increased in FMF patients and MPV was evaluated in these patients. Patients who are in inactive period were compared with healthy control group and MPV was found to be higher in patients (p=0.001). It was observed that MPV value had negative correlation with colchicum treatment (p=0.017), and positive correlation with delay in treatment (p=0.001). They did not make any interpretation regarding the rise in MPV and proposed that it may indicate the risk of atherosclerosis. Makay et al reported that MPV was lower during an attack of FMF than an attack free period. (p=0.00) In addition, in the study of Arica et al carried out in 2011, MPV values in FMF patients were evaluated at attack and attack free periods and higher MPV was found during attacks. However, the difference was not statistically significant. (p=0.34). When patients either in attack period or in inactive period were compared with healthy control group, MPV value was found to be higher in patients group overall than control group. (p<0.05) It is thought that the absence of exclusion criteria in both studies may have influenced results.

Studies evaluating the relation of disease activity with MPV in the above mentioned diseases may shed light on the issue in spite of their various limitations. In order to evaluate the relation between MPV and inflammation more clearly, further prospective studies on other inflammatory diseases and studies attempting to elucidate other probable mechanisms regulating MPV are required. Whether there is relation between MPV, which is considered a thrombocyte activity index, and DVT was investigated in various studies. In a study carried out by Çay et al in 2012, MPV was found to be

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(p<0.001). Since it has discriminatory power according to ROC analysis, cut off value for MPV was determined to be >8.45 fL (sensitivity 92,% specificity 55%). High level of MPV in association with clinical disease activity may reflect thrombo-cyte activation in BD, which is associated with endothelial damage owing to its vasculitic nature.

In a study carried out by Yüksel et al in 2009, it was found that ulcerative colitis patients had lower MPV than control group and patients with active disease than those with inactive disease. It was proposed that MPV reflected disease activity more accurately than did sedimentation, CRP and leukocyte count. In their study, it was observed that MPV value was low in the presence of uveitis and arthritis, which are extra intestinal involvement sites of the disease. In the present study, MPV changes with ocular and articular involvement was assessed. No significant difference was found between patients who have ocular involvement and those who do not have in terms of MPV values. (p=0.82). When patients with history of arthritis were compared with those without such an history, it was determined that MPV was significantly higher in patients with history of arthritis (p=0.019). However, this finding does not appear to be generalizable since it was obtained disregarding the impact of disease activity as in the study of Yüksel et al.

In the studies carried out on RA and AS patients, MPV values obtained seem to be contradictory. In the study of Kısacık et al in 2008, prior to the initiation of treatment, lower MPV values were observed in RA and AS patients compared to control group. (p<0.001 and p<0.001). When patients were evaluated again two months after treatment, it was established that significant increase occurred in MPV values of RA and AS patients compared to first evaluation (p<0.001 and p<0.001). Regarding disease activity, only in AS patients, a negative correlation was shown at the second month of treatment between MPV and Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) scores.

In the study of Yazıcı et al in 2009 on AS patients, when patients and healthy controls were compared prior to treatment, it was observed that MPV value was higher in AS patients. Following six months of treatment (conventional treatment and anti-TNF treatment) significant reduction was seen in MPV value. In addition, it was stated that MPV correlated with disease activity evaluated with BASDAI score. Actually, in a study conducted by Gasparyan et al, MPV value was found to be higher in RA patients than control group (p<0.001) and in the patient group, those with hypertension had even higher MPV value. (p=0.003). It was suggested that this rise may be an indicator of increased cardiovascular risk. MPV was also evaluated in patients with familial Mediterranean fever (FMF), an autoinflammatory disease. As BD is considered as an auto-inflammatory disease by some authors, we also aimed to find out whether MPV results similar to those in FMF patients would be obtained.

A study carried out by Çoban et al in 2008 was based upon the findings that MPV increase was associated with cardiovascular disease risk. Atherosclerosis risk was suggested to be increased in FMF patients and MPV was evaluated in these patients. Patients who are in inactive period were compared with healthy control group and MPV was found to be higher in patients (p=0.001). It was observed that MPV value had negative correlation with colchicum treatment (p=0.017), and positive correlation with delay in treatment (p=0.001). They did not make any interpretation regarding the rise in MPV and proposed that it may indicate the risk of atherosclerosis. Makay et al reported that MPV was lower during an attack of FMF than an attack free period. (p=0.00) In addition, in the study of Arica et al carried out in 2011, MPV values in FMF patients were evaluated at attack and attack free periods and higher MPV was found during attacks. However, the difference was not statistically significant. (p=0.34). When patients either in attack period or in inactive period were compared with healthy control group, MPV value was found to be higher in patients group overall than control group. (p<0.05) It is thought that the absence of exclusion criteria in both studies may have influenced results.
higher in the patient groups with acute, chronic and subacute DVT than control group (respectively 8.6±1.3 and 7.9±0.5 and p<0.001). Yet, in this study, the effect of cardiovascular risk factors on MPV was not evaluated\(^2\). In a study conducted in Norway in 2010, it was reported that high MPV may be an indicator of risk for venous thromboembolism (VTE) in the absence of any triggering factor\(^2\). In the present study, in order to evaluate whether there is a relation between venous thrombosis, which is a type of vascular involvement in BD, and MPV, patients were subdivided into those with history of venous thrombosis and those without it after being divided into active and inactive patient groups. Among active patients, there was no significant difference between patients with history of thrombosis and those without it in terms of MPV, while among inactive patients, those with history of thrombosis had significantly higher MPV values than the other group. (p=0.024). It may be stated that MPV mirrors the predisposition to thrombosis in these patients whether they are in active period or inactive one. Therefore, this data may help to identify patients with high risk. Further prospective studies with larger series may help to determine whether MPV may have such a predictive value prior to venous thrombosis. In the present study, in active group, MPV was not different between patients with an history of thrombosis and those without it, which may be attributed to the fact that MPV is already high in the presence of active disease. Actually, in the evaluation made in inactive patients, MPV was found to be significant (p=0.024). Another important characteristics of BD distinguishing it from other vasculitic diseases is that thrombosis occurs frequently. Based upon the data obtained in previous studies, it has been suggested that MPV is a marker of thrombotic risk\(^2\)\(^6\)\(^7\).

In conclusion, it was established that, in the presence of active disease in BD, MPV also increases significantly as well as ESR, CRP and the number of leukocytes in association with acute inflammation. In addition, it was found that in the presence of active disease, the number of thrombocytes was lower, albeit within normal range, indicating negative correlation between MPV and the number of thrombocytes. Further prospective studies with larger samples and addressing the factor playing role in the regulation of MPV and early detection of disease activity will help to take necessary measures and to guide treatment.

References


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