Introduction

Behçet’s disease (BD) is a multisystemic inflammatory disease characterized by exacerbation and periods of remission. The pathogenesis of the disease appears to be complex and multifactorial; hence, it remains unknown, but vascular endothelial pathologies, hypercoagulability and clotting disorders have been proposed as possible causes\(^1\). Distinctively in BD, the occlusion can affect both veins and arteries, and in histopathological examination a nonspecific inflammation is seen\(^2\).

It was observed that episodes of thrombosis tend to occur in younger patients with BD as well as during periods of increased disease activity\(^3\).

Recurrent aphthous stomatitis (RAS) is a chronic painful ulceration of the oral mucosa with an unknown etiology, but possible initiating factors include trauma, infections, immune mechanisms, or genetic predisposition\(^4\). Furthermore, RAS that recurs more than three times a year is a major criterion for the diagnosis of BD and is usually the initial sign of this disease.

References


The mean platelet volume (MPV) shows the average size of platelets in the blood\(^6\). Thus, an increase in platelet volume and size indicates platelet function and activation, which is also related to thrombosis and inflammation\(^6\). Correlations between increased MPV values and some thrombotic diseases, such as deep vein thrombosis, acute myocardial infarction, or acute ischemic cerebrovascular events, have previously been reported\(^9\). In other inflammatory processes such as rheumatoid arthritis (RA) and ankylosing spondylitis (AS), it was reported that the MPV was significantly higher, reflecting, in addition, disease activity\(^8\).

Until now, in previous studies MPV levels were reported to be higher in BD patients than controls, but in different patients with active and inactive phase of BD, and no correlation has been found regarding the disease activity\(^6,10\). However, the differences in MPV levels during the active and inactive phase of BD have not been compared in the same individuals. Here, we aimed to determine whether the MPV can be used as a marker for BD in disease activation and severity, therefore, we performed this study to compare the same patients’ MPV levels during the active and inactive periods of BD with RAS and control group.

**Materials and methods**

The diagnosis of BD was based on the clinical criteria established by the International Study Group of Behçet’s Disease in 1990\(^11\). If at least two clinical findings were present at the time of diagnose or during follow up, the BD was considered to be active. Patients with typical painful oral ulcers that recurred at least 3 times a year without any organ involvement of BD were diagnosed as RAS.

The files of BD and RAS patients who were followed up in our Behçet’s Disease Center between February 2006 and February 2014 were reviewed, and data of the 33 BD patients who had routine complete blood cell (CBC) count, erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) results during the active and the inactive periods of the disease were included in this study. They were compared with age- and gender matched 35 RAS patients with active ulcers at the time of testing, and 60 patients who were diagnosed with non-inflammatory skin disorders (e.g. telogen effluvium) served as controls. The median age of BD patients, RAS patients and controls were 29 (18-63) years, 36 (18-65) years and 30 (18-65) years, respectively (p=0.405). The male to female ratio was 13:20 in BD group, 13:22 in RAS group and 23:37 in control group (p=0.982). The baseline demographic findings of the BD patients are shown in Table 1.

<table>
<thead>
<tr>
<th>Males/Females</th>
<th>13/20</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>32.50 (± 12.88)</td>
</tr>
<tr>
<td>Duration of the disease (years)</td>
<td>9.85 (± 6.44)</td>
</tr>
<tr>
<td>Family history</td>
<td>9</td>
</tr>
<tr>
<td>Mucocutaneous involvement</td>
<td>33</td>
</tr>
<tr>
<td>Positive pathergy test</td>
<td>14</td>
</tr>
<tr>
<td>Vascular involvement*</td>
<td>8</td>
</tr>
</tbody>
</table>

**Table 1:** Demographic properties of the Behçet’s Disease patients (n=33).

* Vena cava superior syndrome (n=1), Pulmonary thromboembolism (n=1), Transverse sinus thrombosis (n=1), Venous thrombosis of Sigmoid sinus (n=1), Deep venous thrombosis (n=1), superficial thrombophlebitis (n=3).

Patients with BD, RAS or controls who were using aspirin or any other drugs that could have had an influence on platelet functions were excluded from the study. In addition, patients or controls with diabetes mellitus, peripheral vascular disease, cardiovascular disease, cerebrovascular events, hematological disorders, inflammatory bowel disease, or malignancies were also not included. This study was approved by the Ufuk University Local Ethics Committee (Approval number: 280520142).

According to our laboratory protocol, all of the blood samples were taken by venipuncture between 8 and 11 a.m. after a fasting period of 12 hours, and these were then analyzed within one hour of receipt. The CBC parameters from routine tubes containing ethylene diamine tetra acetic acid (EDTA) were studied, and the analyses were performed using the Abbott CELL DYN 3700 automated hematology analyzer (Abbott Laboratories, Abbott, IL, USA). In our laboratory, the reference range for the MPV, ESR and CRP levels are ranged from 6.9 to 10.4 fL, 0.01 to 20 mm/h and 0.01 to 5 mg/L, respectively.

**Statistical analysis**

The Predictive Analytics Software (PASW) version 18.0 for Windows (SPSS Inc., Chicago, IL,
USA) was used for all analyses. To determine data distribution, a single-sample Kolmogorov-Smirnov test was performed, and one-way analysis of variance (ANOVA), Wilcoxon and Mann-Whitney U tests were used to compare the groups. In addition, p values of less than 0.05 were considered to be statistically different.

Results

A comparison of the groups with regard to their laboratory findings is presented in Table 2. In the active period of BD, the MPV levels were slightly higher than those in RAS and control groups (ANOVA, p=0.148); however, MPV levels were significantly higher during the active period than inactive period of the BD (Wilcoxon test, p=0.007). Moreover, comparison of MPV levels in 8 BD patients with vascular event history yielded that, during the active period of the disease (9.3 fl; 7.7-10.5) MPV levels were statistically significantly higher than inactive period (7.3 fl; 6.8-5) (Wilcoxon test, p=0.012). Also, in the active period, the MPV levels of the same 8 BD patients with vascular event history (9.3 fl; 7.7-10.5) were higher than 25 patients without vascular involvement (8.6 fl; 5.93-13.10), however, no statistically significant differences were found between the groups (Mann-Whitney U test, p=0.165).

Table 2: Comparison of laboratory findings between Behçet’s disease, RAS, and controls.

<table>
<thead>
<tr>
<th>Results (median)</th>
<th>BD (n=33)</th>
<th>RAS (n=35)</th>
<th>Control (n=60)</th>
<th>p1</th>
<th>p2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin (g/dL)</td>
<td>13.6</td>
<td>14.1</td>
<td>14.1</td>
<td>13.7</td>
<td>0.928</td>
</tr>
<tr>
<td>WBC (10³/µL)</td>
<td>7.60</td>
<td>6.70</td>
<td>5.90</td>
<td>6.27</td>
<td>0.074</td>
</tr>
<tr>
<td>Platelet count (x10¹¹/L)</td>
<td>252.00</td>
<td>247.00</td>
<td>239.00</td>
<td>250.15</td>
<td>0.532</td>
</tr>
<tr>
<td>MPV (fL)</td>
<td>8.60</td>
<td>8.30</td>
<td>8.40</td>
<td>8.40</td>
<td>0.217</td>
</tr>
<tr>
<td>ESR (mm/h)</td>
<td>13</td>
<td>9</td>
<td>10</td>
<td>7</td>
<td>0.186</td>
</tr>
<tr>
<td>CRP (mg/L)</td>
<td>7.38</td>
<td>1.96</td>
<td>1.32</td>
<td>1.00</td>
<td>0.027*</td>
</tr>
</tbody>
</table>

Table 2: Comparison of laboratory findings between Behçet’s disease, RAS, and controls.

BD: Behçet's disease; RAS: Recurrent aphthous stomatitis; WBC: White blood cell; MPV: Mean platelet volume; ESR: Erythrocyte sedimentation rate; CRP: C-reactive protein; p1: Comparison of inactive phase of BD with RAS and control groups p2:Comparison of active phase of BD with RAS and control groups

Discussion

The elevation in MPV is accepted as a sign of inflammation and is also associated with platelet activation. Larger platelets are more reactive and contain more dense granules filled with higher amounts of active substances (e.g. thromboxane A2) (12). The exact pathogenic mechanism associated with the formation of vascular lesions in BD remains unclear, but endothelial dysfunction is thought to have a major role in the pathogenesis of thrombosis (13). Akar et al. reported that the platelets in the BD patients were more reactive than in the controls, which contributed to the thrombotic tendency (14). Additionally, IL-6 levels were shown to be elevated in BD patients with an active disease, which can also induce megakaryopoiesis and releasing of bigger platelets from the bone marrow (15, 16). Therefore, we hypothesized that platelet activation might be related with the pathophysiology of BD since this disease is prone to inflammation and thrombosis. We also thought that because the MPV is routinely measured in CBC counts, it could have served as a practical biomarker of disease activation.

To the best of our knowledge, no studies exist that have compared the MPV levels in the same individuals during the active and inactive periods of BD. In their study, Acikgoz et al. concluded that there were no significant differences in the MPV levels between the active (8.20 fl) and inactive (8.08 fl) groups of BD, and that it was significantly higher in the BD patients (8.14 fl) than the controls (7.48 fl) (9). Similarly, Ekiz et al. also determined that the MPV levels in the active phase (8.21 fl) of BD were not significantly higher than the inactive phase (8.44 fl), although, they reported significantly higher MPV levels in patients with BD and RAS than controls (10). Balta et al. found significantly higher MPV levels in the BD patients (8.86 fl) in their study compared with the controls (8.39 fl), and MPV was also significantly increased in BD patients in the active phase (9.07 fl) than those in inactive phase (8.40 fl) (11).

In our study, the MPV levels in the active period of BD were found to be high but not statistically higher than the RAS and control groups. Therefore, we concluded that it was not possible to use our MPV results to discriminate BD from RAS and controls. However, this difference might be related to the relatively small sample size in our study.
Also, we showed that, the MPV levels were significantly increased during the active period (8.6 fL) of the disease compared to the inactive period (8.30 fL), probably because of the fact that we had studied MPV levels in the same individuals during the active and inactive periods of the disease. On the contrary, Lee et al. found lower MPV levels in patients with BD (9.97 fL) than in the control group (10.5 fL)\(^{19}\). We also found that MPV levels in the inactive phase were even lower than RAS and control group. Our finding might help us to understand the discrepancy of Lee et al.’s study, because disease activity was not taken into consideration in their study. Also, Turkcu et al. reported lower MPV levels in the active uveitis phase of BD than in the controls\(^{20}\). These results might differ from our study because non-ocular involvement of the disease was not compared in their study, and ocular involvement of the disease might also have additional etiopathogenetic factors than non-ocular involvement.

Our patients with vascular involvement had significantly higher levels of MPV during the active period of the disease than the inactive period, but the MPV levels in these patients with vascular involvement during the active period was not statistically higher than patients without vascular involvement. Here, we cannot show statistically significant results due to relatively little number of patients with vascular involvement (n=8), but Acikgoz et al. found that the MPV was statistically higher in BD patients with thrombosis (8.45 fL) than in those without thrombosis (7.96 fL)\(^{20}\). These results also showed that increased platelet reactivity was to blame for the development of vascular lesions associated with BD. In contrast, Lee et al. and Ekiz et al. determined that there were no significant differences with regard to thrombosis\(^{10, 19}\). Their results might differ from our study due to the fact that MPV levels were not compared in the same individuals during the active and inactive periods of the disease.

The discrepancies between previous studies could also stem from the fact that anticoagulants (EDTA or citrate) might potentially affect platelet size, and that measurements from various types of automated cell count analyzers have shown the disparity in MPV levels\(^{20}\). The main limitation of this study was its retrospective design. Hence, a non-standardized delay after venipuncture could affect the MPV results\(^{21}\). Another limitation was the relatively small number of patients included in our study.

In conclusion, our results showed that MPV levels of active BD patients did not differ from RAS and controls, and also MPV levels in patients with vascular involvement during the active period was not statistically higher than patients without vascular involvement. However, MPV was significantly increased in BD patients during active phase compared to inactive phase, and also in BD patients with vascular event history MPV levels during the active period of the disease were statistically significantly higher than inactive period. These results show us that, MPV levels are not useful to discriminate BD from RAS, and the elevation of MPV levels should be considered for each patient individually. In conclusion, our results suggest that during follow-ups the MPV measurements can be valuable while predicting to determine disease activity. In addition, we might say that an elevation in the MPV could alarm clinician as the patient’s BD is getting activated and that there might be an increased risk of vascular involvement with BD.

References

10) Ekiz O, Balta I, Sen BB, Rifaioglu EN, Ergin C, Balta S, et al. Mean platelet volume in recurrent aphthous...


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