Evaluation of Inflammation Parameters in Philadelphia Negative Chronic Myeloproliferative Neoplasia Patients

Tuba Hacibekiroglu1*, Sema Akinci2, Abdulkadir Basturk3, Besime inal4, Tekin Guney2, Sule Mine Bakanay2, Imdat Dilek2

Abstract

Background: Chronic myeloproliferative diseases are clonal stem cell diseases which occur as a result of uncontrollable growth and reproduction of hematopoietic stem cells, which are the myeloid series source in bone marrow. Recent studies have suggested that chronic inflammation can be a triggering factor in the clonal change in chronic myeloproliferative neoplasia (CMPN). In our study, we evaluated the existence of a chronic inflammation process in our Philadelphia negative (Ph-)CMPN patients using inflammation parameters in combination with demographic, laboratory and clinical characteristics of the patients. Materials and Methods: Demographic characteristics, clinical and laboratorial data, and thrombosis histories of 99 Ph-CMPN patients, who were diagnosed at our outpatient clinic of hematology in accordance with WHO 2008 criteria, were analyzed retrospectively, with 80 healthy individuals of matching gender and age included as controls. Complete blood counts, sedimentation, C reactive protein (CRP), JAK V617F gene mutations, abdomen ultrasound images and previous thrombosis histories of these patients were retrospectively analyzed. Results: Ph-CMPN and healthy control groups included 99 and 80 cases, respectively. PV, ET and MF diagnoses of patients were 43 (%43.4), 44 (44.4%) and 12 (12.1%), respectively. JAK V617F gene mutation was found to be positive in 64 (71.1%) of all cases and in 27 (65.8%), 32 (82%), 5 (50%) of the cases in PV, ET and PMF groups, respectively. Thrombosis was determined as 12 (12%) in the entire group, 12.5% in the JAK V617F negative and 15.3% in the positive patients, with no statistical significance (p=0.758). No significant difference was observed between patients with and without previous thrombosis history in respect to hemogram parameters, sedimentation and CRP (p>0.05), neutrophil to lymphocyte ratio (NLR), erythrocyte distribution width (RDW), mean platelet volume (MPV) and sedimentation levels of the patient.

Keywords: Chronic inflammation - chronic myeloproliferative neoplasia
particularly with elevated leukocyte levels and JAK2 V617F mutation was indicated. Recent studies have suggested that chronic inflammation can be a triggering factor for the clonal change in CMPN. (Hassellbalch., 2013). It is suggested that chronic inflammation process inflicts damage in the stem cell structure by inducing chronic oxidative stress in bone marrow, and a microenvironment posing high level of risk for mutation can trigger oxidative damage in hematopoietic stem cell DNA ((Hassellbalch., 2013). In addition to sedimentation and C-reactive protein, which are among commonly used chronic inflammation indicators, recent studies have suggested that RDW, MPV and NLR levels, which were associated with inflammation in these studies, are other indicators for its existence (Gasparyan et al., 2011; Guo et al., 2013). In our study, we evaluated the existence of a chronic inflammation process in pathogenesis of chronic myeloproliferative neoplasia by using these 5 inflammation parameters, which have not been studied in combination so far, in CMPN patient group.

Materials and Methods

Demographic, clinical and laboratory data, abdomen ultrasound imaging and thrombosis histories of 99 regularly followed Ph-CMPN patients, who were diagnosed at our outpatient clinic of hematology in accordance with WHO 2008 criteria, were retrospectively analyzed. 80 gender and age matched healthy individuals were included as control group. JAK2 V617F mutations, complete blood counts, and levels of sedimentation and CRP at the time of diagnosis were retrospectively analyzed. Additionally, neutrophil to lymphocyte ratio (NLR) was determined for each case. The correlations of obtained data with thrombosis history in cases with CMP were evaluated.

Statistical analysis

SPSS 17 (Chicago IL, USA) was used for all of the statistical analyses. Compliance of data with normal distribution was evaluated with One Sample Kolmogorov Smirnov test. Results were presented as mean±standard deviation in parametric data and as minimum, maximum and median in non-parametric data. Chi-square test for categorical data and Independent Sample T and Mann Whitney-U tests for parametric and non-parametric data comparison between groups were used respectively. Pearson correlation analysis was carried out for correlative laboratory parameters in CMPN patients. Values below P < 0.05 were accepted to be statistically significant. Binary logistic regression analysis was carried out as independent variable analysis.

Results

Out of the 99 patients included in the analysis, 49 cases were female and 50 cases were male with a mean age of 59.8 (26-87). F/M ratio in the healthy control group consisted of 80 individuals was 36/44 with a mean age of 59.8 and there was no significant difference between two groups in respect to age and gender dispersion (p>0.05) (Table 4). PV, ET, PMF diagnoses were detected as 43 (43.4%), 44 (44.4%) and 12 (12.2%) in patient sub-groups, respectively. Clinical and laboratorial characteristics of patient group and sub-groups were found as specified in Table 1. JAK2 V617F was positive in 64 cases (71.1%) in patient group, and the group with the highest positivity was essential thrombocythemia group with a value of 82%. Splenomegaly and hepatomegaly were most commonly observed in PMF group. Thrombosis was detected in 12 (12.1%) of all patients and its highest incidence was in PMF. (Table 1) Vein thromboses (primarily portal and splenic vein thrombosis) were more common in PMF group while arterial thrombosis (primarily myocardia infarction and cerebrovascular incidents) were more common in PV and ET groups. Thrombosis was detected in 15.3% of the patients with positive JAK2 V617F.
Table 4. Hemogram Parameters in Patient and Control Groups

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Patient (n±SD)</th>
<th>Control (n±SD)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>59.8</td>
<td>53.5</td>
<td>0.161</td>
</tr>
<tr>
<td>Gender(F/M)</td>
<td>49/50</td>
<td>36/44</td>
<td>0.845</td>
</tr>
<tr>
<td>WBC (K/uL)</td>
<td>10.89±6.52</td>
<td>6870±4.1688</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Neutrophil (K/uL)</td>
<td>7853±1078</td>
<td>1875±611</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Lymphocyte (K/uL)</td>
<td>2165±1078</td>
<td>4658±1405</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hemoglobin (g/dl)</td>
<td>15.2±3.2</td>
<td>14.2±0.76</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Thrombocyte (K/uL)</td>
<td>620.000±</td>
<td>271.600±</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>MPV (fL)</td>
<td>9.5±1.4</td>
<td>7.1±0.76</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>RDW (%)</td>
<td>16.8±3.5</td>
<td>13.2±0.68</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>NLR</td>
<td>4.3±3.6</td>
<td>0.43±0.15</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Sediment (mm/sec)</td>
<td>14</td>
<td>5</td>
<td>0.005</td>
</tr>
<tr>
<td>CRP (mg/dl)</td>
<td>0.5</td>
<td>2</td>
<td>0.1</td>
</tr>
</tbody>
</table>

mutated and in 12.5% of the patients with negative JAK2 V617F, which has no significant difference (p=0.758) (Table 2). Upon comparison of complete blood count parameters, and levels of sedimentation and CRP between patients with and without previous thrombosis, no statistically significant difference was observed between the parameters as it can be seen in Table 3. Laboratory data of patient and control groups were respectively mean white blood count (WBC) 10.897-6.870 K/uL, hemoglobin (Hgb) 15.2-14.2 g/dl, thrombocyte 620.000-271.600 K/uL, RDW %16.8-13.3, NLR 4.3-0.43, MPV 9.5-7.1 fL, sedimentation 14-5 mm/sec and CRP 0.5-2 mg/dl, all of which excluding CRP were found to be elevated with statistical significance in patient group (Table 4). MPV was determined to be the independent predictive value of CMPN patients.

Discussion

Chronic myeloproliferative diseases are a disease group in hematologic malignities which requires long-term close monitoring. Cause of mortality or morbidity is generally thromboembolic incidents, hemorrhage or leukemic transformation. Positivity of JAK2 V617F mutation and leukocytosis were proven to be factors which increase thrombosis risk by a number of studies. (Takaya et al., 2014; Payzin et al., 2014) The fact that protease and oxygen radicals released with leukocyte activity inflict damage in endothelial cells, leukocyte adhesion molecule release and increased adhesion of leukocyte and thrombocyte on endothelial cell are given as the underlying prothrombotic factors (Kremyanskaya et al., 2013). Conducted researches indicated that JAK2 gene mutation can be correlated with elevated leukocyte activation and activated neutrophils can bind thrombocytes, and the release of tissue factor can be triggered with this binding (Kremyanskaya et al., 2013). In our study, no correlation of JAK2 gene mutation with leukocytosis and thrombosis was observed.

As specified in literature, JAK2 V617F mutation was most commonly found positive in polycythemia vera with 90-95% among Ph- CMPN cases. In our study, it was found positive with 82% in patients with essential thrombocytosis in contrast to the literature. Recently, chronic inflammation process has been mentioned in chronic myeloproliferative diseases. Conducted studies indicate the increased risk of premature atherosclerosis and thrombosis as a result of the process during which proinflammatory cytokines secreted from increased leukocytes and thrombocytes due to clonal myeloproliferation trigger inflammation. CRP was accepted as inflammatory marker in the literature and their role in thrombosis risk within myeloproliferative diseases was researched (Barbui et al., 2009; Barbui et al., 2011; Landolfi et al., 2011). Furthermore, additional gene mutations induced by cytokines, chemokines and oxygen radicals released in chronic inflammation are thought to play an active role in cancer development and metastasis.

We evaluated inflammation process by comparing sedimentation, CRP, MPV, RDW and NLR levels, which were taken as a basis, not only in the thrombosis group but also within the entire group itself with healthy controls. In contrast to the literature, these values did not have any difference between patients with and without a history of thrombosis. However, the analysis conducted in healthy controls produced significantly elevated levels excluding CRP in the patient group. Several studies conducted in different areas researched the roles of MPV, RDW and NLR in inflammation. Elevated levels of MPV, RDW and NLR in conditions such as infection, thrombosis and cancer which are tables of inflammation are indicated in the literature (Kitaza et al., 2013; Karaman et al., 2013; Unal et al., 2013; Yu Q et al., 2013; Aktas et al., 2014; Gunay et al., 2014). Our findings are not surprising if we consider myeloproliferative diseases as the inflammatory disease of hematopoietic stem cell and evaluate inflammation the trigger of CMPNs as suggested by Haaselbalch et al. Likewise, these indicators, which were demonstrated to be significant in terms of inflammation by conducted studies, were also found to be elevated in our study.

As a result, our study supports that an inflammation process is the triggering and maintaining factor in CMPN. We believe that this hypothesis should be analyzed through extensive multicenter studies with a high number of cases.

References

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