Single Chromosomal Abnormalities in Philadelphia-negative Chronic Myeloproliferative Disorders

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Abstract. Background: In Philadelphia-negative chronic myeloproliferative disorders (CMPD), increased proliferation with effective maturation of the myeloid lineage is present, while peripheral leukocytosis, thrombocytosis or elevated red blood cell mass are found. This group of disorders includes polycythemia vera (PV), essential thrombocythemia (ET) and idiopathic myelofibrosis (IMF). Furthermore, cases that cannot be clearly defined are regarded as unclassified CMPD. In Philadelphia-negative CMPD, recurrent cytogenetic abnormalities occur, but no specific abnormality has been defined to date. Chromosomal abnormalities detected in a neoplastic disease as a sole anomaly are of major importance, possibly constituting primary changes implicated in the initiation or progression of the neoplastic process. The aim of this study was to investigate the frequency and the type of single chromosomal changes in Philadelphia-negative CMPD patients. Materials and Methods: By conventional cytogenetics, 245 Philadelphia-negative CMPD cases at diagnosis were investigated for the frequency and the type of single chromosomal aberrations. Results: Seventeen patients presented single chromosomal changes. These aberrations were, according to frequency, +8 (in 3 PV cases, 2 IMF and 2 unclassified myeloproliferative diseases), +13 in 3 cases (IMF, ET and unclassified myeloproliferative disease), monosomy 10 in 2 PV cases, monosomy 14 in one ET patient, +3, –4 and del(11)(q13) in 1 unclassified myeloproliferative disease each and monosomy 7 in 1 IMF case. Conclusion: It is unclear whether these abnormalities found at the time of diagnosis play a role in CMPD. However, since an isolated chromosomal abnormality may be implicated in the initiation of the neoplastic process, the documentation of more cases of CMPD with single abnormalities at the time of diagnosis would facilitate the identification of candidate genes involved in the neoplastic process.

Chronic myeloproliferative disorders (CMPD) are clonal disorders of hematopoietic stem cells. An increased proliferation with effective maturation of the myeloid lineage is present, while peripheral leukocytosis, thrombocytosis or an elevated red blood cell mass are found. This group of disorders includes chronic myeloid leukemia (CML), polycythemia vera (PV), essential thrombocythemia (ET) and idiopathic myelofibrosis (IMF). Today, CML is considered a separate entity defined by the t(9;22)(q34;q11) translocation, which results in the production of the BCR/ABL fusion protein. An overlap is often seen between distinct categories of CMPD with progression from one disease to another, while they also share a tendency to progress to bone marrow fibrosis or transform into acute leukemia. From a clinical point of view, the differentiation between the different types of CMPD and reactive disorders often presents difficulties, especially in cases of thrombocytosis or fibrosis. Furthermore, cases that cannot be clearly defined are regarded as unclassified CMPD, while some cases show features of both myeloproliferative and myelodysplastic syndrome, such as chronic myelomonocytic leukemia (CMML) proliferative type (1-3).

In Philadelphia-negative CMPD, recurrent cytogenetic abnormalities occur but specific patterns of chromosomal aberrations have so far not been detected. The spectrum of cytogenetic aberrations is heterogeneous ranging from numerical gains and losses to structural changes including unbalanced translocations. The most common chromosomal abnormalities are 20q–, 13q–, 12p–, +8, +9, partial duplication of 1q, and gains in 9p. Cytogenetic analysis of CMPD may contribute to establishing the diagnosis of a malignant disease and may also serve as predictor of disease outcome. It is considered that some chromosomal abnormalities may be responsible for the initiation or progression of a neoplastic disease, whereas

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it was suggested that certain abnormalities may be influenced by environmental factors (1, 3-12).

The aim of this study was to investigate the frequency and the type of single chromosomal changes in Philadelphia-negative CMPD patients at the time of diagnosis. Since single chromosomal abnormalities might be primary changes implicated in the initiation of the neoplastic process, we focused on these abnormalities comparing our findings with those found in the literature.

Materials and Methods

On reviewing patients of Philadelphia-negative CMPD cytogenetically studied in our laboratory, 245 patients with an analysis at the time of diagnosis were found. Among them, 85 had PV, 73 ET, 49 IM and 38 unclassified myeloproliferative diseases. Patients with both myeloproliferative and myelodysplastic syndrome, such as CMML, were not included in this study. None of the patients had received chemotherapy before the cytogenetic study. Additional clinical data or laboratory findings were not available for most of the cases studied. Bone marrow samples from all 245 patients had been processed for cytogenetic analysis at the time of first diagnosis by a direct culture of cells and a G-banding technique. As many cells as possible were analyzed in each case and no fewer than 15. An abnormal clone was defined as two or more metaphases with either the same structural anomaly or the same extra chromosome, or as three or more metaphases lacking the same chromosome. Karyotypes were described according to the International System for Human Cytogenetic Nomenclature (ISCN 1995) (13). Since single chromosomal abnormalities might be primary changes implicated in the initiation of the neoplastic process, we focused on these abnormalities.

Results

Among the 245 cases of CMPD cytogenetically studied, only 17 presented single chromosomal abnormalities (Table I). Six of them had unclassified myeloproliferative disease, five PV, four IM and two ET. Among patients with unclassified myeloproliferative disease two presented trisomy 8, while trisomy 13, monosomy 4, trisomy 3 and del(11)(q13) was observed in one case each. Among cases with PV, three presented trisomy 8 and two monosomy 10. Two IMF patients had trisomy 8, while trisomy 13 and monosomy 7 was observed in one IMF case each. In two ET patients (14), monosomy 14 and trisomy 13 were found.

Discussion

In Philadelphia-negative CMPD recurrent cytogenetic abnormalities occur, but no specific abnormality has been defined to date. Cytogenetic analysis of CMPD has an important role in establishing the diagnosis of a malignant disease and may be informative for disease outcome. In contrast to leukemias, chromosomal gains and deletions rather than recurrent balanced translocations constitute the prominent cytogenetic finding in CMPD. The most common chromosomal abnormalities are 20q−, 13q−, 12p−, +8, +9, partial duplication of 1q and gains in 9p. It is thought that loss of genetic material may lead to loss of tumor suppressor genes, whereas gains of chromosomal material may lead to a gene dosage effect. Chromosomal

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Table I. Single chromosomal abnormalities in 17 cases with Philadelphia-negative chronic myeloproliferative disorders.

<table>
<thead>
<tr>
<th>Case no.</th>
<th>Disease</th>
<th>Karyotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Polycythemia vera</td>
<td>47,XX,+8</td>
</tr>
<tr>
<td>2</td>
<td>Polycythemia vera</td>
<td>47,XX,+8</td>
</tr>
<tr>
<td>3</td>
<td>Polycythemia vera</td>
<td>47,XY,+8</td>
</tr>
<tr>
<td>4</td>
<td>Idiopathic myelofibrosis</td>
<td>47,XX,+8</td>
</tr>
<tr>
<td>5</td>
<td>Idiopathic myelofibrosis</td>
<td>47,XX,+8</td>
</tr>
<tr>
<td>6</td>
<td>Unclassified myeloproliferative disease</td>
<td>47,XX,+8</td>
</tr>
<tr>
<td>7</td>
<td>Unclassified myeloproliferative disease</td>
<td>47,XX,+8</td>
</tr>
<tr>
<td>8</td>
<td>Idiopathic myelofibrosis</td>
<td>46,XY[16]/47,XY,+13[3]</td>
</tr>
<tr>
<td>9</td>
<td>Essential thrombocytthemia*</td>
<td>46,XX[17]/47,XX,+13[3]</td>
</tr>
<tr>
<td>10</td>
<td>Unclassified myeloproliferative disease</td>
<td>46,XY[14]/47,XY,+13[4]</td>
</tr>
<tr>
<td>11</td>
<td>Polycythemia vera</td>
<td>45,XX,-10</td>
</tr>
<tr>
<td>12</td>
<td>Polycythemia vera</td>
<td>45,XY,-10</td>
</tr>
<tr>
<td>13</td>
<td>Unclassified myeloproliferative disease</td>
<td>47,XX,+3</td>
</tr>
<tr>
<td>14</td>
<td>Idiopathic myelofibrosis</td>
<td>46,XY[14]/45,XY,-7[4]</td>
</tr>
<tr>
<td>15</td>
<td>Unclassified myeloproliferative disease</td>
<td>46,XY[14]/45,XY,-4[4]</td>
</tr>
<tr>
<td>16</td>
<td>Essential thrombocytthemia *</td>
<td>46,XX[18]/45,XX,-14[4]</td>
</tr>
<tr>
<td>17</td>
<td>Unclassified myeloproliferative disease**</td>
<td>46,XX[6]/46,XX,del(11)(q13)[10]</td>
</tr>
</tbody>
</table>

*Previously published (14); **Previously published (21).
abnormalities detected in a neoplastic disease at diagnosis as a sole anomaly are of major importance, possibly constituting primary changes implicated in the initiation of the neoplastic process (1, 3, 6, 7, 9).

By conventional cytogenetics, 245 Philadelphia-negative CMPD cases at diagnosis were investigated for the frequency and the type of single chromosomal abberation. Seventeen patients presented single chromosomal changes. These aberrations were, according to frequency, +8 (in 3 PV cases, 2 IMF and 2 unclassified myeloproliferative diseases), +13 in 3 cases (IMF, ET and unclassified myeloproliferative disease), monosomy 10 in 2 PV cases, monosomy 14 in 1 ET patient, +3, –4 and del(11)(q13) in one unclassified myeloproliferative disease each and monosomy 7 in 1 IMF case.

Trisomy 8 is the most common autosomal numerical aberration seen in myeloid malignancies. The genetic consequence of +8 is unclear, although data suggested that genes on the 8q may be important. CMPD patients with trisomy 8 have a relatively good prognosis, especially those of PV. It was reported that trisomy 8 may persist in PV without further clonal evolution or leukemia development for a long period of time (1, 3-5, 9).

Trisomy 13 as a sole anomaly was found in three of our cases. Abnormalities of chromosome 13 mainly involving deletion of 13q represent a common finding in CMPD. Molecular methods showed that alterations of 13q may be more common than has been previously found by conventional cytogenetics. A common deleted region has been found in patients with myeloid disorders (1, 3, 7).

Interestingly, in contrast to other reports, Al-Assar et al. (15) reported gains in 13q in a high percentage of patients with IMF studied by comparative genomic hybridization (CGH). A number of genes have been mapped on 13q that might be target genes for the development of CMPD (16-17). Trisomy 13 has been described as a recurring abnormality in AML, but it is rarely described in other hematological diseases. Only three patients with CMPD and a +13 have been reported in the literature; all three had a diagnosis of myelofibrosis and they presented trisomy 13 as a sole anomaly (18-20). The presence of an isolated trisomy 13 found in three of our cases at the time of diagnosis is of interest and may support the hypothesis that this abnormality is implicated in the development of the neoplastic process. However, additional cases of +13 need to be described with the follow-up of patients to better understand the possible role of this aberration in CMPD.

Del(11)(q13) was found in one case with unclassified myeloproliferative disease (21). This patient had a poor clinical course and a very poor response to therapy. Abnormalities of 11q are among the most common found in myeloid malignancies and often harbor a breakpoint at 11q23. Del(11)(q13) was reported as a sole anomaly only in a few cases of myeloid malignancies (19, 21). Concerning CMPD, interstitial deletion of 11q13q21 as a sole anomaly has been previously described in only one case of myelofibrosis with myeloid metaplasia (22).

Monosomy 7 was found in one case with IMF. Abnormalities of chromosome 7 including –7 and/or 7q– have been frequently described in myeloid malignancies and are usually accompanied by other complex chromosomal changes. Several genes have been mapped on 7q that may function as tumor suppressor genes. Monosomy 7 in PV patients may signal the terminal phase of the disease. Moreover, it was reported that abnormalities of chromosome 7 are detected more frequently at the time of leukemic transformation in IMF patients, but this observation was not confirmed by other reports. Patients with IMF and chromosomal abnormalities –7 and/or 7q– seem to have an inferior outcome (3, 23-24).

Monosomy 10 was found in the present study in two PV patients. This abnormality has been described in only two cases of IMF and in seven cases of PV, but in combination with other changes. Monosomy 4 found in one of our cases of unclassified myeloproliferative disease has been previously reported in only 2 cases of PV with a complex karyotype. Trisomy 3 is an uncommon abnormality in CMPD, described in a few only cases, but not as a sole anomaly. An isolated monosomy 14 found in one of our cases with ET has never been described in CMPD (19).

Recently, a novel mutation, JAK2V617F, has been described in CMPD. This finding represents the most important advance in our understanding of the molecular mechanisms underlining the pathogenesis of CMPD and contributing to classification and management of patients. Nevertheless, cytogenetic analysis continues to play an important role in CMPD, while recently reported studies investigated CMPD patients both cytogenetically and for JAK2 mutation detection (3, 25, 26).

In the present study, single chromosomal abnormalities were found in 17 patients with CMPD. It is unclear whether these abnormalities, found at the time of diagnosis, play any role in the neoplastic process. However, since an isolated chromosomal abnormality may be implicated in the initiation or the progression of the neoplastic process, the documentation of more cases of CMPD with single abnormalities at the time of diagnosis would facilitate the identification of candidate genes involved in the neoplastic process.

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References


