inv(16)(p13q22) in Chronic Myelogenous Leukemia in Blast Phase

A Clinicopathologic, Cytogenetic, and Molecular Study of Five Cases

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Abstract

Blast phase (BP) in chronic myelogenous leukemia (CML) frequently is accompanied by cytogenetic abnormalities in addition to t(9;22)(q34;q11.2). We describe 5 patients with CML in blast phase (CML-BP) in which t(9;22) and inv(16)(p13q22) were identified by conventional cytogenetics, with confirmation of BCR/ABL and CBFβ/MYH11 by fluorescence in situ hybridization. The morphologic findings at the time of BP resembled de novo acute myeloid leukemia (AML) carrying inv(16)(p13q22), with abnormal eosinophils in the bone marrow and monocytosis in the peripheral blood in all cases. In 1 patient, inv(16)(p13q22) and abnormal eosinophils were detected in the bone marrow 2 months before CML-BP. The clinical course of these patients was similar to patients with CML-BP without evidence of inv(16)(p13q22). These cases illustrate that inv(16)(p13q22) is a form of cytogenetic evolution that rarely occurs in patients with CML at the time of BP. In this setting, unlike de novo AML, inv(16)(p13q22) in CML-BP is not associated with a favorable prognosis.

Acute myeloid leukemia (AML) with abnormal eosinophils was first reported in 1983,1 and in the same year, its association with the inv(16)(p13q22) was established.2 In the revised French-American-British classification of AML published in 1985, this neoplasm was designated as M4 Eo and was defined by the presence of a myelomonocytic blast population and bone marrow eosinophilia with abnormal eosinophils.3 The abnormal eosinophils have mixed eosinophilic and large, basophilic granules that are positive for naphthol AS-D chloroacetate esterase and the periodic acid–Schiff reaction. The World Health Organization classification published in 2001 recognizes this neoplasm as a distinctive clinicopathologic and molecular entity designated as acute myelomonocytic leukemia with eosinophilia (AMML Eo).4 This neoplasm is included in the group of acute myeloid leukemias with recurrent genetic abnormalities. Patients with AMML Eo are known to have a favorable prognosis.

The inv(16)(p13q22) and the much less common t(16;16)(p13;q22) are characteristic of AMML Eo. The breakpoints and genes involved in these abnormalities have been cloned. The core binding factor β (CBFβ) gene at 16q22 and the myosin heavy chain gene (MYH11) at 16p13 are both disrupted and recombined to create a novel fusion gene, CBFβ/MYH11.5 This fusion gene can be detected routinely by using a variety of methods, most commonly, conventional cytogenetics, fluorescence in situ hybridization (FISH), and reverse transcription–polymerase chain reaction (RT-PCR).

Chronic myelogenous leukemia (CML) is a myelo-proliferative disease characterized by the presence of the t(9;22) (q34;q11.2), also known as the Philadelphia chromosome.
Patients with CML usually progress through 3 stages of disease. Initially, they present in chronic phase, characterized by a high WBC count and hypercellular bone marrow composed of maturing granulocytes. In this phase the t(9;22) is the only cytogenetic abnormality. Eventually, the tempo of the disease quickens into a stage similar to acute leukemia, also known as blast phase (BP) or blast crisis. This transformation frequently is preceded by an intermediate stage known as accelerated phase. Transition to BP often is accompanied by the appearance of additional chromosomal abnormalities besides Ph, in other words, cytogenetic clonal evolution. The most commonly observed abnormalities include an extra Ph, trisomy 8, and isochromosome 17q. Rarely, chromosomal translocations characteristic of certain types of de novo AML can occur in CML-BP, such as the t(8;21)(q21;q21) and the t(15;17)(q22;q12).

We describe 5 patients with CML-BP carrying both inv(16)(p13q22) and t(9;22)(q34;q11). In all cases, the morphologic findings resembled AMML Eo at the time the inv(16)(p13q22) was detected.

Materials and Methods

We searched the files of the Cytogenetics Laboratory at our institution for cases with both inv(16)(p13q22) and t(16;16)(p13;q22) and t(9;22)(q34;q11.2) between January 1993 and July 2004. Five cases were identified. The medical records and all relevant laboratory reports (pathologic, cytogenetic, and molecular) were reviewed. Four patients had CML-BP. Each of these patients previously had a diagnosis of CML in chronic phase, and conventional cytogenetics studies had shown the t(9;22)(q34;q11.2) without the inv(16)(p13q22) or any other cytogenetic abnormalities. One patient presented with AML with 42% blasts associated with the t(9;22)(q34;q11.2) and a high WBC count (768,000/µL [768 x 10⁹/L]). This case is consistent with de novo CML-BP. The clinical and pathologic findings are summarized in Table 1.

![Table 1](image)

Summary of Clinical Features

<table>
<thead>
<tr>
<th>Case No./Sex/ Age (y)</th>
<th>Initial Diagnosis</th>
<th>Diagnosis at Time of inv(16)</th>
<th>Splenomegaly</th>
<th>Interval From Original Diagnosis to BP (mo)</th>
<th>Response to Therapy</th>
<th>Outcome (mo From Onset of Blast Phase)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/F/43</td>
<td>CML-CP</td>
<td>CML-BP</td>
<td>Present</td>
<td>11</td>
<td>No response</td>
<td>Died (3)</td>
</tr>
<tr>
<td>2/M/48</td>
<td>CML-CP</td>
<td>CMLAP</td>
<td>Present</td>
<td>30</td>
<td>CR†</td>
<td>Alive (7)</td>
</tr>
<tr>
<td>3/F/61</td>
<td>CML-BP</td>
<td>CML-BP</td>
<td>Present</td>
<td>0</td>
<td>Persistent CMLBP</td>
<td>Died (7)§</td>
</tr>
<tr>
<td>4/M/47</td>
<td>CML-CP</td>
<td>CML-BP</td>
<td>Present</td>
<td>8</td>
<td>CR†</td>
<td>Died (15)‡</td>
</tr>
<tr>
<td>5/F/36</td>
<td>CML-CP</td>
<td>CML-BP</td>
<td>Present</td>
<td>7</td>
<td>No response</td>
<td>Died (1)</td>
</tr>
</tbody>
</table>

AP, accelerated phase; BP, blast phase; CML, chronic myelogenous leukemia; CP, chronic phase; CR, complete remission.

* Based on cytogenetics findings alone.
† Bone marrow/stem cell transplantation.
‡ From the time of relapse with inv(16).
§ Died of graft-vs-host disease.

![Table 2](image)

Summary of Pathologic and Immunophenotypic Findings of Bone Marrow at the Time of Chronic Myeloid Leukemia, Blast Phase

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Bone Marrow Blasts (%)</th>
<th>Blast Morphologic Features</th>
<th>Blast Immunophenotype</th>
<th>Bone Marrow Eosinophils (%)</th>
<th>Abnormal Eosinophils Present in Bone Marrow</th>
<th>Chloroacetate Stain Reaction in Abnormal Eosinophils</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>30</td>
<td>Myelomonocytic</td>
<td>CD13, CD14, CD33, CD34, CD117, HLA-DR</td>
<td>22</td>
<td>Yes</td>
<td>Positive</td>
</tr>
<tr>
<td>2</td>
<td>20</td>
<td>Myeloid</td>
<td>CD13, CD33, CD117, HLA-DR</td>
<td>30</td>
<td>Yes</td>
<td>Positive</td>
</tr>
<tr>
<td>3</td>
<td>20</td>
<td>Myeloid</td>
<td>CD13, CD33, CD117, HLA-DR</td>
<td>5</td>
<td>Yes</td>
<td>Positive</td>
</tr>
<tr>
<td>4</td>
<td>40</td>
<td>Myelomonocytic</td>
<td>CD13, CD33, CD64, HLA-DR</td>
<td>11</td>
<td>Yes</td>
<td>ND</td>
</tr>
<tr>
<td>5</td>
<td>70</td>
<td>Myeloid</td>
<td>ND</td>
<td>20</td>
<td>Yes</td>
<td>ND</td>
</tr>
</tbody>
</table>

ND, not done.

Flow Cytometric Immunophenotyping

Four-color flow cytometric immunophenotypic analysis was performed on bone marrow aspirate samples using a FACSCalibur instrument (BD Biosciences, San Jose, CA). Incubation of cells with monoclonal antibodies at 4°C was followed by RBC lysis with NH₄Cl for 10 minutes and washing with phosphate-buffered saline solution. Cells were resuspended and fixed with 1% formaldehyde. The panel of monoclonal antibodies included CD45 (conjugated with peridinin-chlorophyll-α-protein), CD2 (fluorescein isothiocyanate [FITC]), CD3 (allophycocyanin [APC]), CD7 (FITC or phycoerythrin [PE]), CD13 (PE), CD14 (APC), CD19 (FITC or APC), CD33 (APC), CD34 (FITC), CD38 (APC), CD64 (PE), CD65 (PE).
(Caltag, Burlingame, CA), CD117 (PE), and HLA-DR (FITC). All antibodies except those otherwise specified were purchased from BD Biosciences. For each antibody, appropriate negative levels were determined by comparison with an isotype-matched control sample.

Conventional Cytogenetics and FISH

Metaphase cells from bone marrow aspirate samples were cultured for 24 and 48 hours using previously described methods.11 A methanol–glacial acetic acid fixation method was used for obtaining metaphase cells. The cell suspensions were dropped on air-dried slides, subsequently prepared, placed overnight in a 60°C oven, and G-banded (GTG) by conventional methods. We analyzed 20 metaphases.

FISH analysis was performed on each case using a freshly dropped slide from a harvested bone marrow aspirate specimen or a G-banded slide for metaphase mapping. Analysis for BCR/ABL and CBFβ/MYH11 was performed using commercially available LSI-BCR/ABL ES and LSI-CBFB dual-color probes (Vysis, Downers Grove, IL) and an inv(16) DNA probe (for metaphase cells only) (Oncor, Gaithersburg, MD). The LSI-CBFB probe was used for cases 1 through 3, and the inv(16) probe was used for cases 4 and 5. The slides were pretreated with 2× sodium saline citrate, pH 7.0, for 30 minutes at 37°C, followed by serial ethanol dehydrations in 70%, 85%, and 100% for 2 minutes each. Further probe denaturation and hybridization were performed according to the manufacturer’s instructions. A total of 200 interphases or 10 metaphases were analyzed using a fluorescent microscope (Carl Zeiss, Thornwood, NY). In our laboratory, the LSI-BCR/ABL assay is considered positive when BCR/ABL fusion cells are greater than 1.25% and the LSI-CBFB assay is considered positive when CBFβ/MYH11 fusion cells are greater than 2.7%. Any metaphase with a split signal on the chromosome 16 was considered positive for inv(16).

Reverse Transcription–Polymerase Chain Reaction

RT-PCR assays for the detection of BCR/ABL (4 cases) or CBFβ/MYH11 (3 cases) transcripts were performed as described previously.9,12 Total RNA was extracted from bone marrow aspirate specimens using Trizol reagent (Gibco-BRL, Gaithersburg, MD) according to the manufacturer’s instructions. Reverse transcription was performed on 1 to 2 µg of total RNA using random hexamers and Superscript II reverse transcriptase (Gibco-BRL). The resulting complementary DNA was subject to PCR to amplify BCR/ABL fusion transcripts in an ABI PRISM 7700 Sequence Detector (Perkin Elmer/Applied Biosystems, Foster City, CA) using the following primers: forward primer 1 bcr-b2: 5’-ACAGCATCCCGCTGACCAT-3’, forward primer 2 bcr-e1: 5’-GCAAGACCGGCAGATCT-3’, reverse primer abl-a2: 5’-NED-CGAGCGCCTCCTCACTCAGA-3’, and bcr abl-2a: 5’-6FAM-CCTGAGGCTCAAAGTGCAGTGC-TACTGG-TAMRA-3’ (Perkin Elmer/Applied Biosystems). For the detection of CBFβ/MYH11, PCR was performed using the primers INV A (5’-AAGACTGGATGTGATGGGCT-3’) and INV B (5’-CTTGGACTTCTCAGCTC-3’) in a PE 9600 thermal-cycler (Perkin Elmer, Wellesley, MA).

Amplified products were analyzed on 2% agarose gels stained with ethidium bromide, transferred onto positively charged nylon membranes (Genescreen Plus, Perkin Elmer), and hybridized with a biotin-labeled probe INV16 (MYH) (5’-TCTGGAGTGGTATGGGCA-3’) followed by detection with the Photostar chemiluminescence detection kit (New England BioLabs, Beverly, MA) according to the manufacturer’s instructions. A segment of the ABL gene was coamplified as an internal control for both assays.

Report of Cases

Clinical information for the 5 patients is summarized in Table 1.

There were 3 women and 2 men with a median age of 47 years (range, 36-61 years). Three patients (cases 1, 2, and 4) had a typical presentation of CML in chronic phase (CML-CP) with insidious onset, increased WBC count, and splenomegaly. Patient 5 had a slightly increased WBC count (13,000/µL [13 × 109/L]) and marked thrombocytosis (2,200 × 103/µL [2,200 × 109/L]) and autopsied with the thrombocytosis (2,200 × 103/µL [2,200 × 109/L]). Patient 3 had a high WBC count of 768,000/µL (768 × 109/L) with 42% blasts at the time of initial diagnosis. All 5 patients had the t(9;22)(q34;q11.2) as the sole cytogenetic anomaly at the time of original diagnosis.

During CML-CP, the patients were treated with hydroxyurea (cases 4 and 5), imatinib mesylate (cases 1 and 2), interferon (case 4), and leukopheresis (cases 2 and 3). At time of CML-BP, patients were treated with various protocols that included cytarabine (cases 1-5), cyclophosphamide (cases 4 and 5), decitabine (case 4), imatinib mesylate and idarubicin (case 3), and topotecan (case 5). Two patients underwent bone marrow (case 4) and peripheral blood stem cell transplantation (case 2) and achieved complete remission. Patient 2 was free of disease 7 months posttransplantation, and patient 4 died secondary to graft-vs-host-disease. Patients treated only with chemotherapy did not have a response and died 1 to 7 months after CML-BP emerged. Autopsy was performed in case 1. Leukemic infiltration in multiple organs and leukemic thromboemboli in the pulmonary arteries were demonstrated.
Results

Morphologic Findings

At the time the inv(16)(p13q22) was detected, 4 patients had CML-BP and 1 patient (case 2) was in hematologic remission with 1% blasts and abnormal eosinophils, with the latter being the only abnormal finding in the bone marrow Image 1A. In 2 months, CML-BP developed and bone marrow examination showed 20% blasts and 30% eosinophils with numerous abnormal eosinophils Image 1B.

The bone marrow (BM) morphologic features at the time of CML-BP with inv(16) closely resembled those of de novo AMML Eo, as summarized in Table 2. The blast count ranged from 20% to 70%; no Auer rods were identified. BM eosinophilia was present, ranging from 5% to 30%, and abnormal eosinophils with basophilic granules were identified in all 5 cases Image 2A. In 3 cases assessed, the abnormal

Image 1 (Case 2) This patient was in hematologic remission at the time inv(16) was detected. A, The only abnormal finding was the presence of abnormal eosinophils in bone marrow aspirate smear (Wright-Giemsa, ×1,000). B, Two months later, blast phase developed and bone marrow examination showed 20% blasts and 30% eosinophils with numerous abnormal eosinophils (Wright-Giemsa, ×1,000).

Image 2 (Case 1) A, Bone marrow aspirate smear of chronic myeloid leukemia in blast phase with inv(16) showing an abnormal eosinophil and a monocytic blast (Wright-Giemsa, ×1,000). B, Chloroacetate esterase stain of bone marrow aspirate smear showing positive staining of an abnormal eosinophil (black arrow). The normal eosinophil precursors are negative (arrowheads), and the neutrophils are strongly positive (white arrow) (×1,000).
EOSINOPHILS WERE WEAKLY POSITIVE FOR CHLOROACETATE ESTERASE AND THE PERIODIC ACID–SCHIFF REACTION. BM MONOCYTOSES WAS PRESENT IN 3 CASES (RANGE, 7%–35%), AND ALL PATIENTS HAD PERIPHERAL BLOOD MONOCYTOSIS (RANGE, 2,900–98,000/µL [2.9–98 × 10⁹/L]). CYTOCHEMICAL ASSESSMENT FOR MYELOPEROXIDASE PERFORMED ON BM ASPIRATE SMERMS SHOWED THAT THE BLASTS WERE POSITIVE IN ALL CASES EXCEPT CASE 3. HOWEVER, IN CASE 3, THE BLASTS WERE SHOWN TO BE OF MYELOID LINEAGE BY IMMUNOPHENOTYPIC STUDIES.

IMMUNOPHENOTYPIC, CYTOGENETIC, AND RT-PCR RESULTS

IN 4 PATIENTS (CASES 1–4), FLOW CYTOMETRY IMMUNOPHENOTYPIC ANALYSIS WAS PERFORMED ON THE BM ASPIRATE MATERIAL AT THE TIME THE INV(16) WAS DETECTED. IN ALL 4 CASES, THE BLASTS WERE POSITIVE FOR CD13, CD33, AND MYELOPEROXIDASE. IN CASES 2 AND 3, THE BLASTS ALSO WERE POSITIVE FOR CD34, CD117, AND HLA-DR; AND IN CASES 1 AND 4, THE BLASTS HAD A MYELOMONOCYCYTIC IMMUNOPHENOTYPE WITH EXPRESSION OF CD14 AND CD64 (CASE 1) OR ONLY CD64 (CASE 4). ALL CASES WERE NEGATIVE FOR CD2, CD3, CD5, CD7, CD10, CD19, CD20, AND TERMINAL DEOXYNUCLEOTIDYL TRANSFERASE.

THE COMPLETE KARYOTYPES FOR EACH CASE ARE LISTED IN TABLE 3. AT THE TIME OF INITIAL DIAGNOSIS, THE PH CHROMOSOME WAS DETECTED IN ALL CASES WITHOUT OTHER CHROMOSOMAL ABNORMALITIES. WHEN THE INV(16)(p13q22) WAS DETECTED, IT WAS THE ONLY ABNORMALITY IN ADDITION TO THE PH IN 4 PATIENTS. IN 1 PATIENT (CASE 3) CYTOGENETIC ANALYSIS OF BM SHOWED A COMPLEX KARYOTYPE, WITH PH AND INV(16) IDENTIFIED IN 13 (65%) OF 20 ANALYZED CELLS, IN ADDITION TO OTHER CHROMOSOMAL ANOMALIES, INCLUDING TRISOMY 8. IN CASE 2, CYTOGENETIC EVIDENCE OF CLONAL EVOLUTION WAS DETECTED IN BM 2 MONTHS BEFORE MORPHOLOGIC EVIDENCE OF CML-BP WAS IDENTIFIED.

IN ALL 5 CASES, THE PRESENCE OF BOTH CHROMOSOMAL ANOMALIES WAS CONFIRMED BY FISH ANALYSIS. THE BCR/ABL NUCLEAR FUSION SIGNALS WERE IDENTIFIED, AS WERE SPLIT SIGNALS USING THE LSI-CBFB OR INV(16) PROBE. IN ALL CASES, THE NUMBER OF CELLS WITH BCR/ABL AND INV(16) SPLIT SIGNALS WERE MORE THAN THE NORMAL RANGE. THE PERCENTAGE OF CELLS WITH BCR/ABL RANGED FROM 69% TO 91% (MEDIAN, 89%), AND THE

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Karyotype at Initial Diagnosis</th>
<th>Karyotype When INV(16) Detected</th>
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<tbody>
<tr>
<td>1</td>
<td>46,XX,t(9;22)(q34;q11.2)</td>
<td>46,XX,t(9;22)(q34;q11.2),inv(16)(p13q22)[20]</td>
</tr>
<tr>
<td>2</td>
<td>46,XX,t(9;22)(q34;q11.2)[20]</td>
<td>46,XX,t(9;22)(q34;q11.2),inv(16)(p13q22)[6]/46,XY[14]</td>
</tr>
<tr>
<td>3</td>
<td>46,XX,t(9;22)(q34;q11.2)[20]</td>
<td>46,XX,t(9;22)(q34;q11.2)[3]/46,XX,t(9;22)(q34;q11.2),inv(16)(p13q22)[7]/47XX,+8,t(9;22)(q34;q11.2)[2]/47XX,+8,t(9;22)(q34;q11.2),inv(16)(p13q22)[4]/46,XX,add(X)(p22.3)[1],t(9;22)(q34;q11.2),del(12)(p11.2),inv(16)(p13q22)[1]/47XX,t(9;22)(q34;q11.2),inv(16)(p13q22),+der(22)[t(9;22)[1]/46,XX[2]</td>
</tr>
<tr>
<td>4</td>
<td>46,XX,t(9;22)(q34;q11.2)[20]</td>
<td>46,XX,t(9;22)(q34;q11.2),inv(16)(p13q22)[25]</td>
</tr>
<tr>
<td>5</td>
<td>46,XX,t(9;22)(q34;q11.2)[17]</td>
<td>46,XX,t(9;22)(q34;q11.2),inv(16)(p13q22)[20]</td>
</tr>
</tbody>
</table>
percentage of cells with inv(16) ranged from 14% to 100% (median, 73%). In case 4, the percentage of cells with inv(16) was not quantified, but most cells were positive.

The RT-PCR assay for BCR/ABL fusion transcripts was positive in all 4 cases assessed, with detection of e13a2 (b2a2) in cases 1, 2, and 5 and both e13a2 and e14a2 (b3a2) in case 3. In 3 cases (1-3), samples were analyzed by RT-PCR for CBFβ/MYH11 fusion transcripts. All 3 cases showed multiple fusion transcripts, with type B predominant.

Discussion

We describe 5 patients with CML-BP in which the inv(16)(p13q22) was detected at the time of blastic transformation. The disease in 4 patients had progressed from CP, and 1 patient had t(9;22)+ AML consistent with de novo CML-BP.

The morphologic features of CML-BP with inv(16) in this study closely resembled those of AMML Eo, as described in the World Health Organization classification. Abnormal eosinophils were present in all 5 cases, associated with BM eosinophilia. In all cases, the blasts were of myeloid lineage, and 2 cases had evidence of monocytic differentiation shown by morphologic features and immunophenotype. Peripheral blood monocytosis was also present in all cases.

In our review of the literature, we identified 12 additional cases of CML in which the t(9;22) and inv(16) were detected (Table 4). These cases included 2 reports of Ph+ AML with inv(16) that, in retrospect, probably are also CML-BP. Including the 5 cases we report, there are a total 17 cases with clinical data available for 16 patients. There were 13 men and 3 women with an age range of 21 to 78 years (median, 45.5 years). In all 10 patients whose disease initially began as CML in chronic (9 patients) or accelerated (1 patient) phase, CML-BP developed when inv(16) was detected. The morphologic and immunophenotypic features of these cases are not reported uniformly.

In 16 cases, the blasts were of myeloid lineage, and, in 1 case, the blasts were of precursor B-cell lineage. BM eosinophilia was present in 13 (87%) of 15 cases, and abnormal eosinophils were observed in 14 (93%) of 15 cases in which their presence was addressed specifically. In 10 (59%) of 17 cases, the blasts exhibited myelomonocytic differentiation (Tables 2 and 4).

All patients with CML described to date in whom the inv(16) was detected developed BP. In 1 patient (case 2, present report), evidence of the inv(16) preceded blast transformation by 2 months, an event not uncommon in other types of clonal evolution occurring in CML but reported only once to date for inv(16). In the other case reported, cytogenetic evidence of inv(16) preceded BP by 3 weeks.

Although cytogenetic evidence of clonal evolution in CML is common as the disease progresses to accelerated or blast phase, its impact on prognosis is, at least in part, dependent on the specific chromosomal anomalies that occur. From our experience and the published cases to date, the inv(16) in CML patients occurs in BP and is associated with an aggressive course. Of the 9 patients with clinical follow-up, only 3 survived for a substantial amount of time following onset of CML-BP, with only 1 achieving clinical remission without BM or stem cell transplantation. None of the patients we describe responded to various chemotherapy regimens, and the only clinical remissions were achieved in 2 patients (cases 2 and 4) following stem cell and BM transplantation, respectively.

The estimated time for progression of CML-CP to more advanced stage (CML, accelerated phase or CML-BP) is 3 to 5 years. In contrast, inv(16) and onset of BP seem to occur...
early in the course of disease in patients with CML. The median interval from the initial diagnosis of CML to detection of inv(16) and onset of CML-BP in all reported patients was 3 months (range, 0-173 months).

To date, this is the first study to assess the type of CBFβ/MYH11 transcripts in cases of CML with the inv(16). At least 8 different CBFβ/MYH11 fusion transcripts have been reported in cases of de novo AMML Eo with inv(16), with type A fusion transcript the most common. Type A has a breakpoint at nt495 in CBFβ and a fusion point on MYH11 at nt1921 and occurs in 78% to 84% of all AMML Eo cases.12,24,25 However, in the 3 cases assessed by RT-PCR in this study, type B transcript was most common, although multiple transcripts were identified in all cases. Type B fusion transcript is rare in de novo AMML Eo with the same breakpoint in CBFβ as type A but with a different fusion point on MYH11 at nt1708.24 We identified only 1 brief report of type B CBFβ/MYH11 fusion transcript occurring in CML-BP.24

Of interest, 2 of the patients we identified had been treated with imatinib (for 14 and 24 months, respectively) before blast transformation with inv(16). A third patient, who presented with CML-BP, received this drug in conjunction with a chemotherapy regimen for 6 months before relapse with inv(16). Additional mutations and clonal evolution (numeric or structural changes in chromosomes 22, 8, and 17) have been described among the mechanisms of resistance of patients with CML treated with imatinib,23,26 resulting in emergence of new clones unresponsive to the drug. The inv(16) may be a rare but distinct pathway of resistance to imatinib therapy in patients with CML.

In summary, inv(16) is a rare occurrence in CML-BP and associated with an aggressive course. Morphologically, CML-BP with inv(16) resembles de novo AMML Eo with BM eosinophilia, abnormal eosinophils, and peripheral monocytosis. If abnormal eosinophils are present in a patient with CML, conventional cytogenetics or FISH studies to assess for the inv(16) seem to be indicated.

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