LETTER TO THE EDITOR

Additional t(1;11)(q21;q23) with mixed lineage leukemia rearrangement in T-blastic crisis of a Ph-positive chronic myeloid leukemia

To the Editor:

Chronic myeloid leukemia (CML) is characterized by the proliferation and the accumulation of myeloid cells and their progenitors. During the initial indolent chronic phase, the Philadelphia chromosome (Ph) is usually the sole cytogenetic anomaly, but as the disease progresses into the accelerated phase, and eventually into aggressive blast crisis (BC), secondary chromosomal aberrations, such as +8, i(17q) and +Ph become frequent (1). These additional chromosomal abnormalities are associated with shorter survival and lower remission rates (2). In addition, molecular abnormalities in fundamental genes that control cell cycle and proliferation program can arise as \( \text{p53, Rb1, Ras, Cmyc, p16, and Aml-Evi-1} \) (3). We describe a case of a patient with T-cell blastic crisis of CML presenting the Ph chromosome and \( \text{t(1;11)(q21;q23)} \) with positive mixed lineage leukemia (\( \text{MLL} \)) gene rearrangement shown by FISH analysis as well as its correlation with the clinical course of the disease.

A 15-yr-old female was diagnosed in October 1999 exhibiting a typical myeloproliferative scenario shown both by peripheral blood and bone marrow with very low leukocyte alkaline phosphatase score. Haematologic parameters were as follows: Hb 9.0 g/dL, platelets \( 595 \times 10^9/L \), Ht 27.2% and white blood cell count \( 402 \times 10^9/L \). No cytogenetic and FISH studies were performed at this time. Initially, the patient have responded to the cytoreduction with hydroxyurea. However, 30 d after therapy, despite an important reduction in leukocyte count, she developed a massive ganglionar bulky disease in cervical and mediastinal regions. Lymph node biopsy exhibited a diffuse lymphoid blastic infiltration. The immunophenotype of peripheral blood and bone marrow cells showed a T-lineage profile with CD45+, CD7+ and cCD3+ without any positive myeloid marker (Becton & Dickinson, San Jose, CA, USA). Cytogenetic analysis of bone marrow cells after GTG banding showed the karyotype 46,XX,t(9;22)(q34;q11)[16]/46,XX,t(1;11)(q21;q23),t(9;22)(q34;q11)[4] according to the International System of Human Cytogenetic Nomenclature (4) (Fig. 1A and B). The molecular analysis of \( \text{bcr-abl} \) rearrangement was done by RT-PCR as previously described (5). It was positive for \( \text{b}_{\text{2a2}} \). FISH analysis of bone marrow cells using the dual color \( \text{MLL} \) probe (LSI \( \text{MLL} \) Dual Color Break Apart Rearrangement Probe – Vysis) showed one fusion signal and two split signals were found in 70% of the cells corresponding to the \( \text{MLL} \) rearrangement (Fig. 1C). The patient had a poor clinical outcome with primary refractoriness to the chemotherapeutic approaches. Although she has been indicated for allogeneic bone marrow transplantation, but 7 months after the diagnosis, the patient died due to resistant disease.

The clinical distinction between BC of CML and de novo Ph in acute leukemia is not always clear. The features used to distinguish the Ph ALL from the CML in BC include the presence of chromosomally normal cells accompanying the Ph clone at diagnosis or later in the disease, as well as the achievement of true haematological and, in some cases, cytogenetic remission (6). Blastic phase of CML shows a slightly different karyotypic pattern of evolution, depending on the myeloid vs. lymphoid nature of blast cells (7). The case reported here is uncommon as the CML in T cell BC is very rare (8). Cytogenetic, immunophenotyping and clinical studies also confirmed the diagnosis. Cytogenetic analysis showed the Ph chromosome in 100% of bone marrow cells and in 40% of these cells an additional chromosomal aberration involving the 11q23 region was observed. FISH analysis revealed the \( \text{MLL} \) gene rearrangement. Rearrangements involving 11q23 are well documented in haematopoietic malignancies (9). In about 50–70% of cases, the molecular

Figure 1 Partial karyotype showing (A) t(9;22)(q34;q11) and (B) additional chromosomal abnormality t(1;11)(q21;q23). (C) FISH analysis using probe covering the breakpoint cluster region of the mixed lineage leukemia (\( \text{MLL} \)) gene, split signals showed the presence of the \( \text{MLL} \) gene rearrangement.
consequence consisted of a disruption of the MLL gene located in 11q23 (10). MLL rearrangements are frequent in the infant acute myeloid leukemia and in secondary leukemia (11). However, 11q23 abnormalities are rare in CML. Only nine cases have been reported in the literature (12–20) (Table 1). In the most of these nine cases were not investigated by FISH or other methods the presence of the MLL rearrangement. Up to now, more than 40 different MLL partner genes have been identified (21). Among them, the AFIq gene, located in chromosome 1, band 21. It has been demonstrated the higher expression of AFIq gene in CD34+ cells and its association with a worse prognosis in myeloid leukemias (22). The t(1;11)(q21;q23) have been reported in a few cases of acute myeloid leukemia (M4/M5, M1 and M2), acute lymphoblastic leukemia and secondary myelodysplastic syndrome (23). We believe that in our case the association between the Ph chromosome and the t(1;11)(q21;q23) with MLL rearrangement played a very important role in the aggressive course of disease evolution with very short survival. As demonstrated by Heim and Mitelman there are cytogenetic pathways in CML evolution with the activation of oncogenes and inactivation of tumor suppressor genes (1). The BCR–ABL might promote secondary molecular and genetic abnormalities that contribute to the expansion of a cell population characterized by enhanced proliferation, increased resistance to apoptosis and differentiation arrest (24). The present case resulted in the co-operation of oncogenes (bcr-abl and AFIq–MLL) in the multistep of leukemogenesis. To our knowledge, this is the first report of CML in T-lymphoid BC showing the Ph chromosome and the t(1;11)(q21;q23), so a larger number of cases with these characteristics is necessary to establish the role of t(1;11) with CML evolution.

### References


### Table 1 11q23 involvement in Ph-positive CML

<table>
<thead>
<tr>
<th>Reference</th>
<th>Sex/age</th>
<th>Status of disease</th>
<th>11q23 anomaly in addition to Ph chromosome</th>
<th>MLL rearrangement</th>
<th>Last therapy</th>
<th>Survival (months) after detection of 11q23</th>
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<tbody>
<tr>
<td>Present study</td>
<td>F/15</td>
<td>Lymphoid BC</td>
<td>t(1;11)(q21;q23)</td>
<td>+ (FISH)</td>
<td>Chemotherapy</td>
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<tr>
<td>Suzuki et al. (12)</td>
<td>M/33</td>
<td>Myeloid BC</td>
<td>t(11;19)(q23;q13.3)</td>
<td>+ (SB and FISH)</td>
<td>Imatinib mesylate</td>
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<td>Royer-Pokora et al. (13)</td>
<td>M/63</td>
<td>CP</td>
<td>t(2;11)(p12;q23)</td>
<td>– (FISH)</td>
<td>Imatinib mesylate</td>
<td>22</td>
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<td>Nishii et al. (14)</td>
<td>F/40</td>
<td>Mixed lineage BC</td>
<td>t(11;17)(q23;q21)</td>
<td>+ (FISH)</td>
<td>Unrelated bone marrow transplantation</td>
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<td>Dierlamm et al. (15)</td>
<td>F/29</td>
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<td>del(11)(q23)</td>
<td>+ (FISH)</td>
<td>Chemotherapy</td>
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<td>Li et al. (16)</td>
<td>M/36</td>
<td>Myeloid BC</td>
<td>t(11;9)(9;22)(q23;p22;q34;q11)</td>
<td>ND</td>
<td>Hydroxyurea</td>
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<td>Dastugue et al. (17)</td>
<td>F/53</td>
<td>Undifferentiated AP</td>
<td>t(9;11)(p22;q23)</td>
<td>ND</td>
<td>Busulfan, hydroxyurea</td>
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<td>M/ND</td>
<td>Myeloid BC</td>
<td>inv(11)(p11q23)</td>
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<td>Cuneo et al. (20)</td>
<td>F/74</td>
<td>Myeloid BC</td>
<td>del(11)(q22q24)</td>
<td>ND</td>
<td>Busulfan</td>
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F, female; M, male; BP, blastic crisis; CP, chronic phase; AP, accelerated phase; FISH, fluorescence 'in situ' hybridization; SB, southern blotting; ND, no described; MLL, mixed lineage leukemia; Ph, Philadelphia chromosome.


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