Philadelphia chromosome-negative acute myeloid leukemia with 11q23/MLL translocation in a patient with chronic myelogenous leukemia

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Abstract: Although defined by the presence of t(9;22), chronic myelogenous leukemia (CML) can have other concurrent additional cytogenetic changes, especially during disease progression. Additional chromosomal changes (ACAs) in CML often occur in Philadelphia chromosome (Ph)-positive cells and are associated with disease acceleration and treatment resistance. Occasionally chromosomal changes occur in Ph-negative cells and this phenomenon is often transient and does not correlate with disease progression. Very rarely myelodysplastic syndrome or acute leukemia can develop in Ph-negative cells. In this study, we report an unusual case of acute myeloid leukemia (AML) with 11q23/MLL translocation emerging from Ph-negative cells in a patient with CML.

Keywords: 11q23; MLL; chronic myelogenous leukemia (CML); Philadelphia chromosome (Ph)-negative AML

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Introduction

Chronic myelogenous leukemia (CML) is defined at molecular level by BCL-ABL1 fusion gene generated from a translocation between chromosome 9q34 and 22q11.2, forming Philadelphia chromosome (Ph) (1). BCR-ABL1 is the only genetic abnormality in 90% of CML cases in chronic phase. As disease progresses, clonal evolution with additional chromosomal changes (ACAs) emerges (2). Approximately 30% of cases in accelerated phase and 50-80% of cases in blast phase have other chromosomal changes besides t(9;22). ACAs often occur in Ph-positive cells (ACAs/Ph+) and are associated with resistance to tyrosine kinase inhibitor (TKI) treatment and disease progression. The most common ACAs include trisomy 8, extra copy of Ph chromosome, i(17)(q10), and trisomy 19. These are so-called major route changes. Other less common ACAs belong to minor route changes.

Occasionally ACAs occur in Ph-negative cells (ACAs/Ph-). Jabbour et al. analyzed cytogenetics in 258 CML patients who were in chronic phase and treated with imatinib (3). After a median follow-up of 37 months, 21 (9%) patients developed chromosomal abnormalities in Ph-negative cells, with −Y and trisomy 8 being the most common. When −Y was excluded, the occurrence rate of ACAs/Ph- was 5%. Although similar cytogenetic changes are associated with myelodysplastic syndromes (MDS) and/or acute myeloid leukemia (AML) in other patients, the emergence of these cytogenetic changes in CML was often transient and disappeared in all but three patients after a median follow-up of 5 months. In a review study by Loriaux et al. (4), the authors summarized 73 CML patients who developed ACAs/Ph− during imatinib treatment. Trisomy 8 was the most common abnormality (53%), followed by chromosome 7 abnormalities (23%). Similar chromosomal changes, also less frequently, have been reported in CML patients treated with interferon (4). Although relatively rare, development of MDS or AML in Ph-negative cells has been reported. Kovitz et al. studied 1,701 CML patients who were treated with imatinib and found that three patients developed AML or MDS in Ph-negative cells (5). Other similar cases
have also been reported (6-15). Overall, −7 and complex cytogenetic changes were the most common chromosomal abnormalities in reported cases of MDS and AML that developed in Ph-negative cells. Occasional cases were diploid (5).

In a recent study of the role of clonal evolution with 11q23/MLL rearrangements in CML (16), we identified an interesting case of AML that emerged from a Ph-negative clone in a patient with a history of CML. No similar case of 11q23/Ph-negative AML has been reported in the literature. Thus in this report, we described this case in detail and discussed the potential mechanisms of the emergence of chromosomal abnormalities in Ph-negative cells.

**Case presentation**

The patient was a 48-year-old man, who initially presented with splenomegaly and leukocytosis with a white blood cell count of 474 K/μL in August, 2010. He was diagnosed with CML, chronic phase. Cytogenetics showed t(9;22)(q34;q11.2)[20]. Molecular study was positive for BCR-ABL1 transcript by real-time reverse transcription polymerase chain reaction (RT-PCR). The patient was treated with several TKIs including nilotinib, imatinib, dasatinib and ponatinib. He responded but experienced intolerance, such as allergy and myelosuppression. In April 2013, the patient presented with pancytopenia with a hemoglobin level of 7 g/dL, white blood cell count of 1.9 K/μL, and platelet count of 10 K/μL. A bone marrow procedure was performed and showed AML with 36% blasts on smears. Flow cytometric immunophenotyping analysis showed blasts were positive for CD13, CD33, CD34 partial, CD38, CD64 subset, CD117, CD123, myeloperoxidase, and negative for CD2, CD7, CD14, CD19, CD22, CD36, CD56, HLA-DR, and TdT. The patient was put on clofarabine, idarubicin, and cytarabine along with ponatinib. He showed a transient response with blast percentage falling to 12% on day 21 of therapy, but progressed to 52% blasts on day 28 bone marrow. The patient died 4 months after emergence of 11q23 clone due to disease progression.

**Discussion**

In this report, we described a unique case of AML developing in Ph-negative cells with 11q23/MLL rearrangement. The summary of its clinicopathological presentation is shown in Table 1. To our best knowledge, this is the first case of 11q23/MLL rearrangement.
developing in Ph-negative cells in a CML patient. Although discussed in the literature, the exact mechanisms that mediate the development of chromosomal abnormalities in Ph-negative cells are not fully understood. One potential explanation is that TKIs may induce chromosomal changes in Ph-negative cells by inhibiting cellular ABL kinase (c-ABL) activity. C-ABL plays an important role in DNA damage repair following DNA damage (17). The inhibition of c-ABL activity may confer cells to be susceptible to DNA damage signals and induce chromosomal changes. Another possibility is that the pathogenesis of CML is a multiple-step event and t(9;22) is not the earliest event, but rather develops from a Ph-negative hematopoietic stem cell clone. The Ph-negative clone has genetic abnormality that not only induces t(9;22) but also other chromosomal changes. When t(9;22) emerges, the growth advantage of CML cells masks cells with other chromosomal changes. During targeted therapy of CML, Ph-positive cells are eliminated and cells with ACAs/Ph- re-emerge.

Rearrangements of 11q23/MLL are common and present in 70-80% of cases of infant acute leukemia (18). In adult, 11q23/MLL rearrangements are less frequent and seen in de novo and therapy-related AML (19). The presence of 11q23/MLL in CML is very rare (16). The translocation partners for 11q23/MLL are diverse with t(9;11)(p22;q23), t(4;11)(q21;q23), and t(11;19)(q23;p13) being the most common (20). T(11;17)(q23;q25) involving SEPT9 gene on 17q25 described in our case has been reported in AML and MDS with a poor prognosis (21). Consistently, the patient reported here showed poor response to chemotherapy and died 4 months after the diagnosis of AML.

Acknowledgements

None.

Table 1 Disease progression from Ph-positive CML to Ph-negative AML

<table>
<thead>
<tr>
<th>Time</th>
<th>Diagnosis</th>
<th>Conventional cytogenetics</th>
<th>FISH</th>
<th>Molecular</th>
</tr>
</thead>
<tbody>
<tr>
<td>08/2010</td>
<td>CML, chronic phase</td>
<td>46,XY,t(9;22)(q34;q11.2)[20]</td>
<td>N/A</td>
<td>BCR-ABL: positive</td>
</tr>
<tr>
<td>04/2013</td>
<td>AML, 36% blasts</td>
<td>46,XY,t(11;17)(q23;q25)[20]</td>
<td>BCR-ABL: 4%</td>
<td>N/A</td>
</tr>
<tr>
<td>05/2013</td>
<td>AML, 63% blasts</td>
<td>46,XY,t(11;17)(q23;q25)[20]</td>
<td>BCR-ABL: Negative</td>
<td>MLL: 86%</td>
</tr>
</tbody>
</table>

Ph, Philadelphia chromosome; CML, chronic myelogenous leukemia; AML, acute myeloid leukemia; FISH, fluorescence in situ hybridization.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Informed Consent: Written informed consent was obtained from the patient for publication of this case report and accompanying images.

References


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