

Acquisition of mixed lineage leukemia rearrangement in a chronic myeloid leukemia patient while on imatinib

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Chronic myeloid leukemia (CML) is a clonal myeloproliferative disorder with a specific genetic abnormality, the Philadelphia chromosome (Ph) translocation t(9;22)(q34;q11) generating the BCR-ABL1 gene fusion. The role of the Philadelphia chromosome translocation t(9;22)(q34;q11) in CML development is well documented and early in the chronic phase of the disease it is the sole chromosome anomaly in the majority of patients with CML. By contrast, disruption of the *mixed lineage leukemia (MLL)* gene located on 11q23 is a recurrent genomic change in acute leukemia and is particularly prevalent in secondary, acute myeloblastic leukaemia (AML), arising following cytotoxic treatment. While the dual combination of 11q23 rearrangement and the Ph translocation has been described in a several CML patients, the rearrangement of *MLL* gene was confirmed only in rare cases.¹⁻⁴ We report a case of combination of the Philadelphia translocation t(9;22)(q34;q11) and t(11;19)(q23;p13.1) in a CML patient who developed accelerated phase of the disease while on imatinib. The patient, a 28-years old female was diagnosed with Ph-positive CML in December 2003. She was treated with hydroxyurea until January 2006 when she was pregnant 26 weeks. Treatment with interferon- α (IFN) was started and she delivered a normal baby, but failed to achieve complete cytogenetic response. From September 2006, she switched to imatinib with an initial dose of 400 mg/day resulting in a complete hematological and cytogenetic remission 6 months later. She maintained her complete response until March 2008, when 25% of the examined metaphases showed the Philadelphia translocation. The initial dose was increased to 600 mg/day, but 6 month later she developed accelerated phase of the disease. A complete blood count revealed: hemoglobin, 8.9 g/dL, leukocyte count $11.6 \times 10^9/L$ (neutrophils 38%, lymphocytes 26%, monocytes 23%, myelocytes 3%, metamyelocytes 6%; blasts 4%) and platelets $125 \times 10^9/L$. Bone marrow aspirate showed hypercellularity with a predominance of myeloid cells including including 17% myeloblasts (promyelocytes 1.5%, myelocytes 22%, metamyelocytes 27%, lymphocytes 7.5%, poly 12%, erythroblasts 13%). Chromosome analysis performed from bone marrow aspira-

tion revealed 100% Ph-positive metaphases and a new cytogenetic finding, a t(11;19)(q23;p13) in 18 out of the 20 examined metaphases. FISH analysis showed 95% BCR-ABL1 positive cells. *MLL* rearrangement was identified using the LSI *MLL* (11q23) Dual Color Break Apart Rearrangement probe (Vysis) revealing 80% of cells with *MLL* rearrangement. The disruption of *MLL* was confirmed in metaphases demonstrating that the distal part of the *MLL* was juxtaposed to the der(19) chromosome, adjacent to the centromeric region (Figure 1). Treatment with Tasigna (400 mg/day) was started, but 2 months later her leukocyte count increased to $100 \times 10^9/L$ with 19% blasts. Serum biochemistry was remarkable for lactatdehydrogenase 1014 U/L and GGT 70 U/L. One month later, she developed fever, progressive dyspnoea and tachycardia and she ultimately died one month later.

While CML progression is frequently accompanied by nonrandom secondary changes, the mechanism(s) responsible for severe block in differentiation and apoptosis remains poorly understood. The acquisition of t(11;19)(q23;p13.1) and its underlying *MLL* rearrangement in our patient is an unusual finding and raises several questions. Firstly, the t(11;19)(q23;p13.1) fusing the *MLL* gene on chromosome 11q23 with the *ELL* (MEN) gene at 19p13.1 is found in a large proportion of AML patients who have been treated by chemotherapy,^{5,6} raising the possibility that the acquisition of *MLL* rearrangement in our patient is the direct consequence of toxic treatment. However; in our case hydroxyurea and interferon was administrated, followed by imatinib therapy for about 2 years, arguing against a direct genotoxic effect of imatinib. In addition, the aberration is not limited to chemotherapy-related mutagenesis and has also been identified in association with de novo myeloid leukemias. Therefore, it is more likely that the cytogenetic evolution observed in our case may represent the changing natural history of CML.

The mechanisms is unclear, however considering *MLL*'s central role as a major player in leukemia, it is likely that the t(11;19)(q23;p13.1) observed in our patient is a form of cytogenetic evolution that play a direct role in CML progression in the same way that results in acute leukemia *de novo*. The critical contribution of *MLL-ELL* fusion protein on the proliferative potential of myeloid progenitors as well as its causal role in the genesis of acute myeloid leukemias was demonstrated using transgenic animal models,^{7,8} though the precise mechanism remains elusive. Further question may be raised regarding the direct or indirect role of *BCR-ABL1* in transition, suggesting that the acquisition of *MLL* rearrangement may be the consequence of genetic insta-

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Key words: CML progression, *MLL* rearrngment, imatinib treatment

Received for publication: 18 May 2011.
Revision received: 7 June 2011.
Accepted for publication: 4 August 2011.

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Hematology Reports 2010; 3:e13
doi:10.4081/hr.2011.e13

bility promoted by BCR-ABL1. Noteworthy, our patient received treatment with hydroxyurea only for about 2 years. While on imatinib therapy, she maintained her complete cytogenetic response for only 18 months. She remained BCR-ABL1 positive by molecular methods during the course of the disease. It is unclear, if and how incomplete supression of BCR-ABL1 tyrosine kinase activity facilitated the development of *MLL* disruption. As *MLL* fusion proteins are dependent on hyperactive signalling from stem cell receptor tyrosine kinases, it can be hypothesed that kinase activity in our case could be of crucial importance. In addition, it has been shown, that the loss of *ELL* function and overexpression of the *MLL-ELL* have anti-apoptotic effects. Therefore, the acquisition of t(11;19) could result in survival of cells that otherwise may have been destined to die, which could contribute to the development and maintenance of imatinib resistance in our patient. A case similar to ours was reported by Suzuki and all,⁹ describing a 33-years old CML patient who was initially treated with interferon- α and hydroxyurea but failed to achieve complete cytogenetic response. One year later, the patient developed blastic phase and a secondary karyotypic change of t(11;19)(q23;p13.3). Treatment with chemotherapy and imatinib was administrated, but the patient failed to achieve remission and died five months later. Similar to our case, the clinical course of this patient was aggressive and unresponsive to imatinib treatment.

The dual combination of 11q23 aberration and Ph is an infrequent phenomenon and has only rarely been reported in CML. These cases have been reported almost exclusively in association with disease acceleration or onset of blast crisis, suggesting the direct role of *MLL* in transformation. As the chromosomal translocation t(11;19)(q23;p13) is a subtle

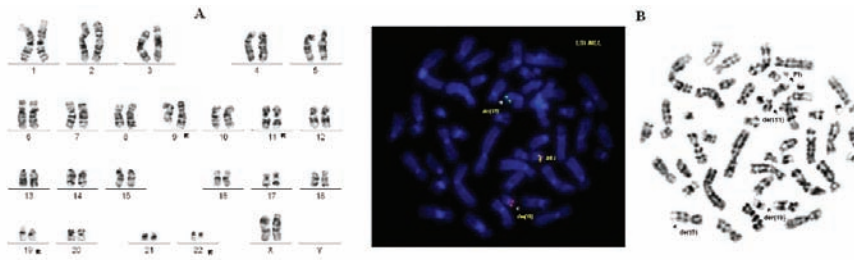


Figure 1. Karyotype of the patient showing simultaneous occurrence of $t(9;22)(q34;q11)$ and $t(11;19)(q23;p13.1)$ (A). FISH using a MLL dual-color, break-apart probe revealing the juxtaposition of the distal part of the MLL gene from chromosome 11 to the der(19) chromosome, adjacent to the centromeric region (red signal) (B).

genetic anomaly and may be easily overlooked by standard cytogenetic analysis, our case further reinforce the importance of FISH in revealing cryptic balanced translocations involved in CML progression.¹⁰

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