

A novel t(2;10) (q31;p12) balanced translocation in acute myeloid leukemia

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Abstract

We describe a case of acute myeloid leukemia M5 showing a balanced t(2;10) (q31;p12) translocation. This has never been described before as the sole cytogenetic abnormality in a bone marrow cell clone at onset. Using fluorescence in situ hybridization with properly designed bacterial artificial chromosome probes, we mapped the breakpoint regions on both derivative chromosomes 2 and 10: der(2) and der(10), respectively. The MPP7 gene, disrupted by the breakpoint on chromosome 10, was juxtaposed upstream of both HNRNA3 and NFE2L2 genes on chromosome 2, without the formation of any fusion gene. Using real-time quantitative polymerase chain reaction, we tested the possible disregulation of any of the breakpoint-associated genes as a consequence of the translocation, but we found no statistically significant alteration. Considering the potential role of this clonal cytogenetic abnormality in leukemogenesis, we speculate that this translocation could have an impact on additional genes mapping outside the breakpoint regions. However, the limited amount of RNA material available prevented us from testing this hypothesis in this present case.

Introduction

The majority of chromosomal rearrangements in acute myeloid leukemia (AML) result in fusion genes or position effects. Indeed, according to the World Health Organization classification of hematopoietic tumors, ¹ a consistent group of aberrations is associated with specific AML subtypes, with both diagnostic and prognostic significance.

In this report, we describe a case of AML (FAB M5 subtype) in which the karyotype displayed a novel t(2;10)(q31;p12) balanced

translocation as the sole cytogenetic abnormality in a bone marrow cell clone at onset.

Case Report

In November 2007, a 42-year old man was admitted to the Department of Hematology and Oncological Sciences of the Seràgnoli Institute, Bologna, northern Italy. He presented with a fever and leukocytosis. Peripheral blood count showed white blood cells 81.7×10⁹/L with 9% neutrophils and 84% blast cells, hemoglobin 12 g/dL, and platelets 89×10⁹/L. Bone marrow aspirate was hypercellular and showed a wide population of medium and large sized cells characterized by a high nuclear/cytoplasmatic ratio and basophil cytoplasm. Immunophenotyping identified a CD13+, CD15+, CD33+, CD117+, MPO7+ population with aberrant expression of CD19. Bone marrow biopsy confirmed a widespread infiltrate with CD68 (PGM1) positive blast cells. A diagnosis of acute monoblastic leukemia was made. Cytogenetic analysis showed the karyotype 47,XY,+8[5]/46,XY,t(2;10)(q33;p12)[4]/46.XY[21]. Mutational analysis was negative for FLT3-ITD, FLT3-TKD and NPM1. In December 2007, induction chemotherapy with fludarabine (50 mg/die for 5 days), cytosine arabinoside (Ara-C) (4 g/die for 5 days), idarubicin (20 mg/die on Days 1, 3 and 5) followed by gemtuzumab-ozogamicin infusion (5 mg on Day 6) was started and a morphological and cytogenetic remission was achieved. The patient later received a first consolidation cycle with idarubicin and Ara-C, and a second consolidation cycle with high-dose Ara-C. In May 2008, bone marrow examination revealed an initial relapse, confirmed by the cytogenetic analysis showing karyotype 47,XY,+8[8]/46, XY[22]. Reinduction chemotherapy was started but the patient showed resistance to conventional chemotherapy. In June 2008, he started therapy with tipifarnib and bortezomib, but he experienced disease progression with peripheral blastosis, anemia and thrombocytopenia. He died 11 months after diagnosis from infectious complications.

Fluorescence *in situ* hybridization analysis mapped the chromosome 2 breakpoint within RP11-25L17 (chr2:177,938,840-178,096,310), precisely within the non-overlapping region (approx. 70 Kb) of this clone with RP11-28M17 (chr2:178,009,023-178,198,838) (Figure 1A). The breakpoint was then located upstream from the *heterogeneous nuclear ribonucleoprotein A3 (HNRNPA3)* gene, encoding a protein involved in alternative splicing,² and the *nuclear factor erythroid 2-like 2 (NFE2L2)* gene, encoding a basic leucine zipper (bZIP) transcription factor.³ Interestingly, both genes had been previously described as deregulated

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in some tumor types. ^{4,5} On chromosome 10, the breakpoint was identified by the splitting signals of RP11-49D12 (chr10:28,369,837-28,539,930) on both der(2) and der(10) (Figure 1A). It encompassed the *palmitoylated membrane protein 7 (MPP7)* gene, encoding a member of the p55 subfamily of MAGUK proteins. ⁶

Neither of these two breakpoint regions has ever been described as being involved in tumorassociated chromosome rearrangements.

To assess the possible impact of this translocation on the *HNRNPA3*, *NFE2L2*, and *MPP7* genes, real-time quantitative polymerase chain reaction assays were performed on the patient's bone marrow (BM) RNA, and compared to 4 AML M5 control cases (without the translocation), as well as to normal BM. We used three reference genes (*HPRT1*, *YWHAZ*, and *SDHA*) and the mean expression value of the control AMLs as calibrator. The results obtained showed that there was no statistically significant change in the expression of any of the genes investigated (Figure 1B).

Discussion and Conclusions

To summarize, we describe for the first time a novel, non-recurrent t(2;10)(q31;p12) translocation in AML which did not lead to any gene fusion or position effects. Remarkably, the molecular consequences of this translocation are to be found outside the breakpoint regions' gene domains. We might speculate





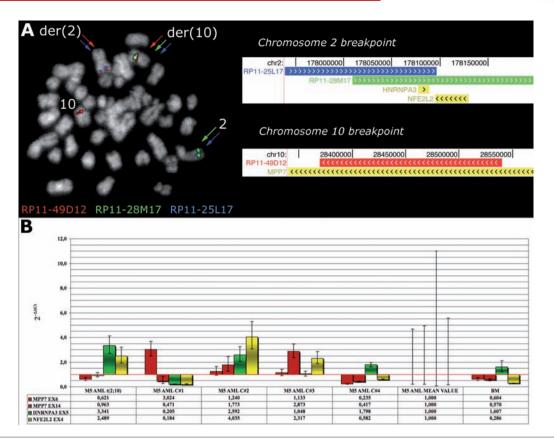


Figure 1. A) Left: Fluorescence in situ hybridization (FISH) results obtained with bacterial artificial chromosome clones delimiting the breakpoint regions on der(2) and der(10). Right: Maps of the breakpoint regions in chromosome bands 2q31.2 (top) and 10p11.23 (bottom), according to the latest release of the UCSC Human Genome Browser (GRCh37/hg19) (February 2009). Genes are indicated by yellow bars. The reported clones have the same color code as the FISH image on the left. B) Expression analyses of exons 6 and 14 of MPP7 (red bars), exon 5 of HNRNPA3 (green bar), and exon 4 of NFEL2L2 (yellow bar) evaluated by real-time quantitative polymerase chain reaction, in the present case [t(2;10)], 4 control akute myeloid leukemia (AML) M5 samples, the mean Ct value of the controls (mean value), and normal bone marrow. The results showed comparable genes transcriptional levels in the patient with t(2;10) compared with the mean Ct value of the 4 M5 AML controls.

that the chromatin relocation due to the t(2;10)(q31;p12) rearrangement might have influenced the expression pattern of additional genes, mapping along both derivative chromosomes 2 and 10. However, we were not able to evaluate this because of the limited amount of RNA material available.

It is not possible to draw clear conclusions about the possible clinical impact of this translocation, also because the rearrangement was not present at relapse. However, on the other hand, the t(2;10)(q31;p12) was the only chromosomal aberration observed in the karyotype of a cell clone in the patient's bone marrow at onset, suggesting it might have an impact on leukemogenesis. Notably, the patient was negative for *FLT3* and *NPM1* mutations, excluding the possibility that this translocation might be a secondary event to this type of alteration. The study of further

AML cases with t(2;10)(q31;p12) would allow us to gain a better understanding of the clinical and molecular impact of this translocation on patient outcome.

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