Letter to the editor

Acute myeloid leukemia (M2) with a cryptic RUNX1/RUNX1T1 t(1;21;8)(p36;q22;q22) variant

The t(8;21) translocation occurs in 5–12% of acute myeloid leukemia (AML) cases, often occurring in the younger population. This translocation fuses the RUNX1 gene (previously AML1) on chromosome band 21q22 to the RUNX1T1 (previously known as ETO) on 8q22, resulting in a RUNX1/RUNX1T1 hybrid transcript on the derivative chromosome 8 [1,2]. According to the World Health Organization, this type of AML is associated with a favorable prognosis [1]. Variant translocations account for approximately 3–4% of all AML-M2 with RUNX1/RUNX1T1 fusion transcripts [3], and the clinical consequences of such variants are less clearly defined. Here, we present a case of AML-M2 with a cryptic three-way translocation, t(1;21;8)(p36;q22;q22).

In January 2009, a 45-year-old African-American man presented with a 2-week history of shortness of breath, fever, chills, and gum bleeding. No lymphadenopathy, organomegaly, or petechiae were noted. Complete blood count revealed an elevated white blood cell count, at 11.1 × 10⁹/L with 69% blasts, 20% segmented cells, 5% bands, 4% lymphocytes, and 2% monocytes. The hemoglobin was decreased, at 8.1 g/L, and the platelet count was also low, at 37 × 10⁹/L.

The morphologic and immunophenotypic features of the bone marrow aspirate and core biopsy were indicative of an expanded population of aberrant myeloid blasts (CD45+, CD34+, CD117+, HLA-DR+, CD13+, CD33+, CD15+, CD19+ and CD56+, MPO+ and negative for nonspecific esterase), overall consistent with AML. Expression of CD19, however, suggested the possibility of AML with t(8;21).

Cytogenetic study of the bone marrow cells revealed the karyotype (described according to ISCN 2005 [4]) as 46,XY,t(1;8)(p36;q22)[19]/46,XY[1] (Fig. 1). Because these results were inconsistent with the morphologic and immunophenotypic reports, FISH analysis was performed using the Vysis LSI AML1/ETO dual-color, dual-fusion translocation probe (Abbott Molecular, Des Plaines, IL). A single RUNX1/RUNX1T1 fusion product was detected on the derivative chromosome 8, a small signal of RUNX1T1 at band 1p36 on chromosome 1, a normal RUNX1 signal in the normal homolog 8, a normal RUNX1 signal on the normal copy of chromosome 21, and a small RUNX1 signal on the second copy of chromosome 21 (Fig. 2).

Further FISH studies using a 1p36 probe (Vysis LSI p58) on previously G-banded metaphases showed that one of the LSI p58 signals was on chromosome 21 (Fig. 3). This led to discovery of the cryptic translocation t(1;21;8) (p36.1;q22;q22). Incorporating the FISH analysis, the karyotype was 46,XY,t(1;21;8)(p36.1;q22;q22).ish t(1;21;8)(RUNX1T1+,D1S2520−,RUNX1−;RUNX1T1−,D1S2520−,RUNX1−;RUNX1T1+,D1S2520−,RUNX1+) [19]/46,XY[1]. Whether the fusion gene RUNX1/RUNX1T1 gene was first developed on the der(8) and subsequently translocated to 1p36, or whether some other mechanisms were involved in this complex chromosomal rearrangement, has not been elucidated.

The RUNX1 gene product is a positive transcription factor for various hematopoietic-specific genes. It binds to a number of promoter and enhancer gene regions, such as CSF1R (colony stimulating factor 1 receptor), CSF2 (granulocyte-macrophage colony stimulating factor; alias GM-CSF), and myeloid myeloperoxidase [2,3,5]. Both RUNX1 and RUNX1/RUNX1T1 recognize the same binding sequence in the DNA, but the hybrid RUNX1/RUNX1T1 fusion protein recruits additional cofactors, mostly repressors, working as a transcriptional repressor for the RUNX1 wild-type target genes and arresting myeloid differentiation [5–10]. In addition to this, RUNX1/RUNX1T1 may selectively regulate the transcription of specific target genes, including colony-stimulating factor (macrophage) (CSF1; previously known as MCSF) and BCL2 [2]. High levels of BCL2 in cells that contain the RUNX1/RUNX1T1 fusion can prolong the cell...
cycle, contributing to the development of leukemogenesis. The synergistic action of the RUNX1 binding factor and the repressing ability of RUNXIT1 promotes the leukemia phenotype [2,3,5,6].

Rearrangements in the distal region of the short arm of chromosome 1 are recurrent aberrations in a broad spectrum of human neoplasias [7–9]. RUNX3 (alias AML2) on 1p36 is one of the three highly conserved AML genes identified in both humans and mice [2]. Involvement of 1p36 in a t(1;21)(p36;q22) has been reported in five previous published cases [8–10]. Minamihisamatsu et al. [11] reported one AML-M2 case with a t(1;8;21)(p36;q22;q22), as well as additional abnormalities, identified by G-banding. This type of translocation, in which a third chromosome is involved, highlights the importance of the RUNX1/RUNXIT1 fusion in the pathogenesis of AML-M2. It is widely accepted that AML patients with the t(8;21)(q22;q22) have a relatively good prognosis with excellent response rates and relapse-free survival [8]. After systemic induction and consolidation chemotherapy, as many as 60% of patients with this translocation remain in complete remission for 5 years [7]. Variants of the classic t(8;21), as in this present case, have been shown to have a similar prognosis—as long as the RUNX1/RUNXIT1 fusion occurs on the derivative chromosome 8. After our patient started on standard chemotherapy treatment with cytarabine and idarubicin, follow-up bone marrow and peripheral blood smear indicated complete remission.

When cryptic variant translocations are suspected or have been identified, complete routine cytogenetic analyses accompanied by FISH studies are warranted, to determine

Fig. 2. (A) Fluorescence in situ hybridization analysis with AML1/ETO probes targeting the RUNX1 gene on chromosome 21 (green) and the RUNXIT1 gene on chromosome 8 (red) reveals an orange/green fusion signal (blue arrow) on the derivative chromosome 8 and an extra copy of the RUNXIT1 gene on chromosome 1. (B) Interphase nuclei showing one big red signal (RUNXIT1), a small red signal (RUNXIT1), a fusion signal for RUNX1/RUNXIT1, and two green signals for RUNX1.

Fig. 3. (A) A G-banded metaphase showing chromosomes 1 and 21. (B) FISH using p58 (1p36) on the same previously G-banded metaphase showing 1 signal for 1p36 on copy of chromosome 1 and the second p58 signal on chromosome 21.
the nature of the variant and to determine its role in the prognostic outcome of a particular hematological malignancy.

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References