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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 11.1×10^9/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 37×10^9/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 *RUNX1T1* 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−, 8204; 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

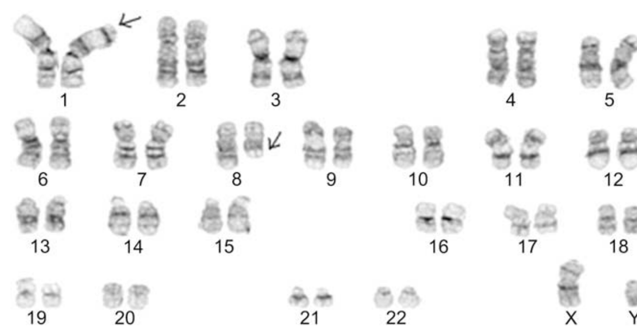

Fig. 1. G-banded karyogram from the patient's bone marrow. Arrows indicate a t(1;8)(p36;q22).

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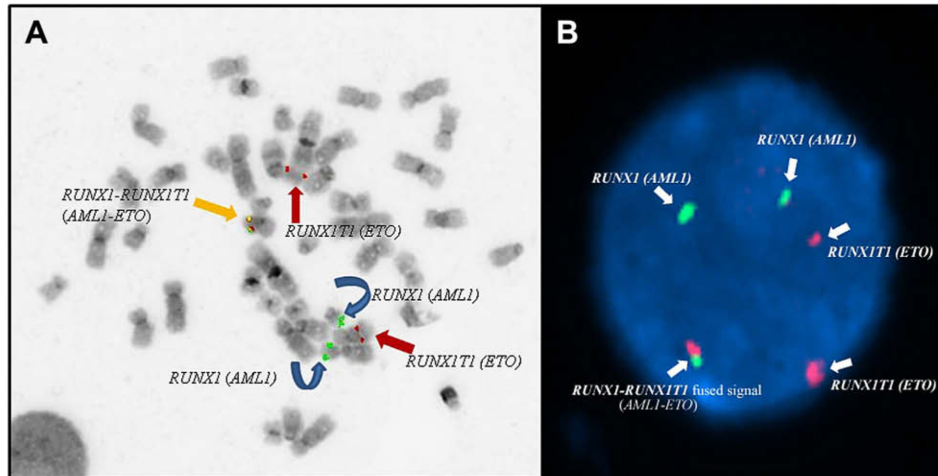

Fig. 2. (A) Fluorescence in situ hybridization analysis with AML1/ETO probes targeting the *RUNX1* gene on chromosome 21 (green) and the *RUNX1T1* gene on chromosome 8 (red) reveals an orange/green fusion signal (blue arrow) on the derivative chromosome 8 and an extra copy of the *RUN1T1* gene on chromosome 1. (B) Interphase nuclei showing one big red signal (*RUNX1T1*), a small red signal (*RUNX1T1*), a fusion signal for *RUNX1*/*RUNX1T1*, and two green signals for *RUNX1*.

cycle, contributing to the development of leukemogenesis. The synergistic action of the *RUNX1* binding factor and the repressing ability of *RUNX1T1* 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*/*RUNX1T1* 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*/*RUNX1T1* 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

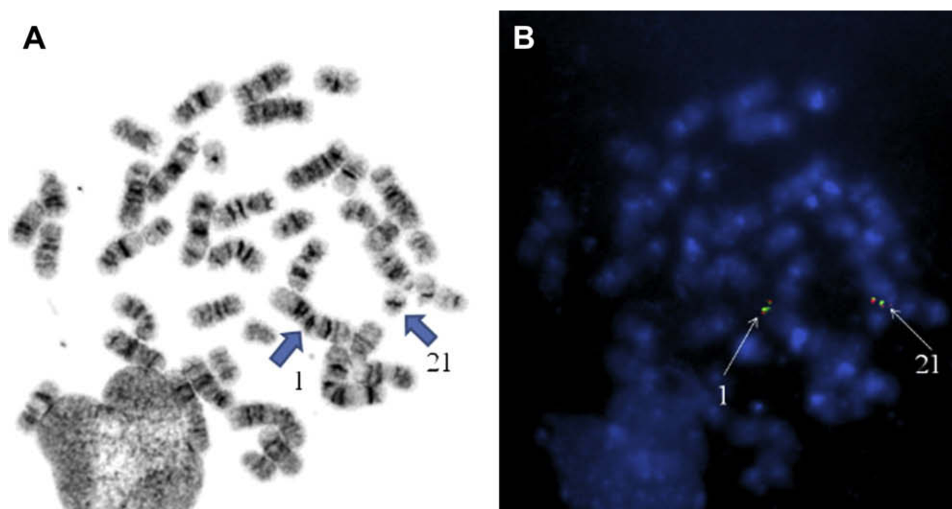

Fig. 3. (A) A G-banded metaphase showing chromosomes 1 and 21. (B) FISH using p58 (1p36) on the same previously G-banded metaphase showing 1 signal for 1p36 on copy of chromosome 1 and the second p58 signal on chromosome 21.

the nature of the variant and to determine its role in the prognostic outcome of a particular hematological malignancy.

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